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Reproductibilité en recherche thérapeutique

Le rôle des financeurs et réanalyse d'essais cliniques via des plateformes de partage de données

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Résumé

Cette thèse explore plusieurs facettes de la reproductibilité de la recherche thérapeutique, en s'intéressant aux initiatives d'ouverture et de partage de données mis en place pour endiguer la « crise de la reproductibilité » que connait la recherche en général et plus particulièrement la recherche biomédicale.

Nous nous sommes intéressés aux politiques de partage de données des financeurs, et à l'impact de ces politiques sur la disponibilité, le partage et la réutilisation des données issues d'essais cliniques. Les indicateurs de disponibilité étudiés relèvent que les politiques actuelles sont inefficaces pour garantir un partage effectif des données. Les financeurs devraient adopter une politique plus forte sur le partage de données, incluant des méthodes d'évaluation, pour s'assurer que les objectifs du partage sont atteints, le tout appuyé par des actions concertées et conjointes avec les acteurs de l'écosystème scientifique tels que les chercheurs et le système éditorial scientifique.

Nous avons également exploré la reproductibilité en recherche thérapeutique. Les données d'un échantillon aléatoire de 62 essais cliniques ont été demandées via des plateformes de partage puis réanalysées. Nous présentons ici les premiers résultats. Les résultats préliminaires portent sur 21 essais cliniques randomisés, dont la reproductibilité inférentielle a été évaluée. Les critères de jugements ont été reproduit à 85.7%.

Les conclusions de cette thèse visent à informer les acteurs de la recherche et à contribuer à l'amélioration des politiques de données ainsi que des pratiques, qui cherchent à faire progresser la recherche thérapeutique vers plus de transparence et une meilleure reproductibilité.

Abstract

This thesis explores several facets necessary for the reproducibility of therapeutic research, by focusing on the initiatives of openness and data sharing put in place to stem the "crisis of reproducibility" experienced by research in general and more particularly biomedical research.

We looked at the data sharing policies of funders, and the impact of these policies on the availability, sharing and reuse of data from clinical trials. The studied availability indicators show that current policies are ineffective in ensuring effective data sharing. Funders should adopt a stronger policy on data sharing, including evaluation methods, to ensure that the objectives of sharing are met, all supported by concerted and joint actions with stakeholders such as researchers and the scientific editorial system.

We also explored reproducibility in therapeutic research. Data from a random sample of 62 clinical trials were requested via data sharing platforms and then re-analysed. Here we present the first results. The preliminary results relate to 21 randomized clinical trials whose inferential reproducibility has been assessed. The primary outcomes of the reanalysed trials were reproduced at 85.7%.

The conclusions of this thesis aim to enlighten research actors and contribute to the improvement of data policies as well as practices, which seek to advance therapeutic research towards more transparency and better reproducibility.

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Publications du manuscrit :

- **Gaba JF**, Siebert M, Dupuy A, Moher D, Naudet F (2020)

Funders' data-sharing policies in therapeutic research: A survey of commercial and non-commercial funders.

PLoS ONE 15(8): e0237464.

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- Pauline Rollando, Céline Parc, Florian Naudet, **Jeanne Fabiola Gaba**

Les politiques de partage de données des financeurs d'essais cliniques en France,

Therapies, Volume 75, Issue 6, 2020, Pages 527-536, ISSN 0040-5957,

https://doi.org/10.1016/j.therap.2020.04.001.

- Naudet F, Siebert M, Pellen C, **Gaba J**, Axfors C, Cristea I, et al. (2021)

Medical journal requirements for clinical trial data sharing: Ripe for improvement.

PLoS Med 18(10): e1003844.

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- **Gaba Jeanne F E**, Maximilian Siebert, Alain Renault, Clara Locher, Bruno Laviolle, David Moher, and NAUDET Florian.

Inferential Reproducibility of Therapeutic Research: A Cross-Sectional Study of Randomized Controlled Trials Available on Major Data-Sharing Platforms

(Date limite de soumission d'article : 8 Décembre 2023, Registered report accepté de principe pour soumission à la Royal Society Open Science)

Autres publications dans le cadre de la thèse (joints en annexe du manuscrit)

- Siebert M, **Gaba JF**, Caquelin L*, et al*

Data-sharing recommendations in biomedical journals and randomised controlled trials: an audit of journals following the ICMJE recommendations

BMJ Open 2020;**10:**e038887. doi: 10.1136/bmjopen-2020-038887

- Siebert, M., **Gaba, J**., Renault, A. *et al.*

Data-sharing and re-analysis for main studies assessed by the European Medicines Agency—a cross-sectional study on European Public Assessment Reports.

BMC Med **20**, 177 (2022). https://doi.org/10.1186/s12916-022-02377-2

- Pellen C, Caquelin L, Jouvance-Le Bail A, **Gaba J**, Vérin M, Moher D, Ioannidis JPA, Naudet F.

Intent to share Annals of Internal Medicine's trial data was not associated with data re-use.

J Clin Epidemiol. 2021 Sep;137:241-249. doi: 10.1016/j.jclinepi.2021.04.011. Epub 2021 Apr 26. PMID: 33915263.

Liste des abréviations

ACM	Association for Computing Machinery
AdAM	Analysis Data Model
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ANR	Agence Nationale de la Recherche
ANRS	Agence nationale de recherches sur le sida
ANSES	Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail
AO	Appels d'Offres
APICIL	Association de Retraites Complémentaires pour l'Industrie et le Commerce Lyonnais
ARSEP	Aide à la Recherche contre la Sclérose en Plaque
ARSLA	Association pour la Recherche sur la Sclérose Latérale Amytrophique
ASCB	American Society for Cell Biology
BMJ	British Medical Journal
CDASH	Clinical Data Acquisition Standards Harmonisation
CDISC	Clinical Data International Standard Consortium
CFDA	China Food and Drug Administration
CHU	Centre Hospitalier Universitaire
CI	Confidence Interval
CIC	Centre d'Investigation Clinique
CMH	Cochran-Mantel-Haenszel
CNRS	Centre National de la Recherche Scientifique
CSDR	Clinical Study Data Request
DGOS	Direction Générale de l'Offre de Soins
DIP	Données Individuelles des Patients
DOAJ	Directory of Open Access Journals
DORA	Declaration on Research Assessment
ECR	Essai Contrôlé Randomisé

EER	Espace Européen de la Recherche
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EPAR	European Public Assessment Report
FAIR	Findable, Accessible, Interoperable and Reusable
FOSTER	Facilitating Open Science in European Research
GIRCI	Groupement Interrégional de Recherche Clinique et d'Innovation
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IFPMA	International Federation of Pharmaceutical Manufacturers and Associations
INCA	Institut national du cancer
INSERM	Institut National de la Santé et de la Recherche Médicale
IPD	Individual Patient Data
LEEM	Les Entreprises du médicament
NEJM	New England Journal of Medicine
NIH	National Institutes of Health
OCDE	Organisation de Coopération et de Développement Economiques
OSF	Open Science Framework
PD	Politique de Partage
PHRC	Programme Hospitalier de Recherche Clinique
PhRMA	Pharmaceutical Research and Manufacturers of America
PLOS	Public Library Of Science
PNSO	Plan National de la Science Ouverte
PSI	Public Sector Information
R&D	Recherche et Développement
RCT	Randomized Clinical Trial
ReiTheR	Reproducibility in Therapeutic Research
SAP	Statistical Analysis Plan
SDTM	Study Data Tabulation Model
SMD	Standard Mean Difference

SOAR	Supporting Open Access for Researchers
TOP	Transparency and Openess Promotion
UK	United Kingdom
USA	United States of America
WHO	World Health Organization
YODA	Yale University Open Data Access

CHAPITRE 1 : INTRODUCTION

Dans le cadre des appels à projets 2022, Horizon Europe, le principal programme de financement européen pour la recherche et l'innovation, a intégré un pilier transversal dont l'une des thématiques de financement est « Réformer et consolider le système de recherche et d'innovation européen », avec un volet sur la science ouverte (dite open science). Ces appels à projets sur la science ouverte visent à financer des projets de recherche collaboratifs européens, qui seront en adéquation avec les sujets suivants : 1- Modélisation et quantification des impacts de la pratique de la science ouverte, 2- Coopération mondiale sur la politique et la pratique des données FAIR (Findable, Accessible, Interoperable and Reusable), 3- Renforcement des capacités pour la publication institutionnelle en libre accès dans toute l'Europe, 4- Confiance de la société dans la science, la recherche et l'innovation, 5- Accompagnement aux évolutions de l'évaluation de la recherche et des chercheurs pour récompenser la pratique de la science ouverte. Ces sujets reflètent l'engagement de l'Europe vis-à-vis de la promotion de la science ouverte et le rôle des financeurs dans la direction des projets de recherche concernant la mise à disposition des données de recherche. La science ouverte peut être définie comme étant l'ensemble des actions permettant un libre accès et une réutilisation des produits de la recherche(1). Les pratiques de science ouverte ont maintenant pris place et ne sont pas étrangers au sein de la communauté scientifique avec des niveaux d'application et d'acceptation différents selon les disciplines. En recherche clinique, plusieurs actions ont été menées par divers acteurs tels que les financeurs, les institutions de recherches et les chercheurs. Les différentes crises de santé publique comme les épidémies d'Ebola, de Zika et actuellement de Covid-19, soulignent la nécessité de faire une science qui respecte les principes d'une science ouverte (2) (3) (4). Pourtant, les pratiques de science ouverte sont encore peu courantes. L'urgence de produire des résultats et des solutions scientifiques de sortie de crise demande une mise en commun de connaissances, un travail collaboratif des chercheurs et des résultats fiables pour une meilleure orientation des décisions politiques de santé (3). Malgré le nombre d'actions mis en place pour en faire une norme, le partage de données demeure très peu réalisé et exploité (5). Le partage de données est un des axes principaux de la science ouverte. Son objectif est de garantir la transparence des résultats et donner la possibilité aux chercheurs extérieurs ou non à l'équipe de recherche initiale, d'établir des confirmations, de réaliser des méta-analyses sur données individuelles ou de proposer de nouvelles hypothèses à partir d'études existantes. La disponibilité des données est la condition *sine qua non* à la réutilisation de résultats existants. Cette possibilité de réutilisation et de vérification est une solution à la crise de reproductibilité (6), conséquence du manque de qualité et d'intégrité des pratiques de recherche, et ce, dans tous

les domaines et plus précisément en recherche biomédicale, menant à une impossibilité de reproduire les études.

1. La science ouverte et la reproductibilité

1.1. La science ouverte : bannière d'une révolution scientifique

Le principe de science ouverte s'est construit autour de la volonté d'une diffusion et d'une réutilisation libres et sans entrave des produits de recherche scientifique (7).

On pourrait situer les prémices de la science ouverte au XVIIème siècle, avec l'avènement des premières revues scientifiques, sous la direction des sociétés savantes(8,9). Jusqu'à cette époque, la diffusion scientifique est très restreinte et souvent cryptée pour en limiter son accès. Cette faible circulation de l'information est devenue un véritable problème. Elle favorise les découvertes simultanées, entraîne des conflits d'attribution de paternité des découvertes comme l'illustre la controverse Newton-Leibniz sur l'invention des calculs différentiels. Améliorer l'accès aux résultats de recherche devient une nécessité d'intérêt commun. Avec la création des sociétés savantes à l'instar de l'Académie des sciences en France en 1666, ou la Royal Society of Science au Royaume Uni en 1660, l'activité scientifique se réorganise et s'institutionalise. La publication de revue scientifique se met en place et constitue le système de divulgation des découvertes scientifiques, qui a conduit au système de revue moderne que nous connaissons aujourd'hui (8). Cependant, l'accès à l'information scientifique est coûteux. Elle constitue une source de dépenses considérable aux chercheurs dont elle est l'essence de leurs travaux. Les tarifs prohibitifs des éditeurs de revue, le développement d'Internet et la philosophie de partage et d'ouverture provenant des logiciels open source, ont fait émerger de nouvelles pratiques de publication, permettant de nouvelles modalités d'accès à la recherche, différentes des méthodes traditionnelles (10) (11).

En 1991, le physicien américain, Paul Gainsparg lance le serveur de prépublications ArXiv, permettant le partage de travaux avant l'évaluation par les pairs et avant publication (pre-prints). L'Initiative de Budapest pour l'Open Access tenue le 14 Février 2002, propose pour fournir un libre accès à la production scientifique : 1- l'autoarchivage par l'auteur dans une archive ouverte conforme aux standards définis par l'Open Archives Initiative, et 2- la publication dans des revues scientifiques alternatives.

Le 22 Octobre 2003, la Déclaration de Berlin, aujourd'hui signée par plus de 480 institutions de recherche, des universités, des institutions de financement de la recherche, élargit le libre accès aux données (12). Elle a été publiée afin de servir de ligne directrice, pour promouvoir Internet comme l'instrument fonctionnel d'une base de connaissances scientifiques mondiales (13). Les objectifs de la déclaration de Berlin relayent les recommandations de Budapest et précise que le « libre accès requiert l'engagement de tout un chacun en tant que producteur de connaissances scientifiques ou détenteur du patrimoine culturel. Les contributions au libre accès se composent de résultats originaux de recherches scientifiques, de données brutes et de métadonnées, de documents sources, de représentations numériques de documents picturaux et graphiques, de documents scientifiques multimédia. » (14).

Les défis constants de la science, l'évolution de la pratique scientifique, les technologies numériques et la révolution de la communication grâce à Internet ont élargis les horizons de l'ouverture de la science. Bartling et Frieske, dans leur livre « Open Science », décrivent une seconde révolution scientifique dont la science ouverte serait le paradigme. La première révolution étant lorsque la publication d'articles scientifiques est devenue le principal moyen de diffusion des connaissances scientifiques. La seconde révolution scientifique serait caractérisée par une culture scientifique, dans laquelle il y aurait un échange de connaissances rapide et une discussion plus soutenue entre les chercheurs, à travers des moyens de diffusion ouverts qui dépassent le cadre des institutions et des réseaux personnels, accrédités par les scientifiques et les autorités compétentes. Les résultats positifs comme négatifs seraient publiés rapidement, au fur et à mesure qu'elles sont produites ; ce qui permettrait d'éviter des expériences inutilement répétées et contribuerait aussi à l'élaboration d'autres projets de recherche (8).

Selon la perception et l'interprétation des différents aspects de cette seconde révolution scientifique, les définitions de la science ouverte varient (1). Les définitions mettent l'accent sur le partage ouvert des connaissances scientifiques le plus tôt possible dans le processus de recherche, sur l'encouragement d'une culture d'ouverture qui inclut l'ensemble du processus de conduite de la science, sur l'encouragement de la collaboration ouverte et l'accès aux connaissances. Il existe une multitude de ressources et d'outils pratiques pour que les avantages de cette nouvelle culture de science ouverte soient une réalité, ce qui peut complexifier sa compréhension et son application. Ramachandran et al (15) l'explique en soulignant que :

*"*le terme « science ouverte » est parfois utilisé de manière interchangeable pour représenter divers principes qui soutiennent l'idée plus large de la science ouverte elle-même. Ces principes

incluent des idées telles que les données ouvertes, les logiciels open source, l'accès ouvert aux revues et la reproductibilité. Par exemple, la reproductibilité, ou la capacité de vérifier les résultats d'un autre scientifique, est rendue possible par les principes des données ouvertes, du code ouvert et des méthodologies transparentes, mais la reproductibilité elle-même n'est pas équivalente à la science ouverte ».

[*the term "open science" is sometimes used interchangeably to represent various principles that support the broader idea of open science itself. These principles include ideas such as open data, open-source software, open journal access, and reproducibility. For example, reproducibility, or the ability to verify another scientist's results, is enabled by the principles of open data, open code, and transparent methodologies, yet reproducibility itself is not equivalent to open science*]

Pour codifier cela, l'initiative Facilitating Open Science in European Research (FOSTER), a élaboré en 2015, une taxonomie de la science ouverte (16). Ils y présentent neufs principaux termes, subdivisés en sous- termes pour mieux décrire les principes de science ouverte. Les neufs termes sont *Open Access, Open Data, Open Reproducible Research, Open Science Definition, Open Science Evaluation, Open Science Guidelines, Open Science Policies, Open Science Projects* and *Open Science Tools*, tous convergeant vers une même vision : une science transparente, avec un processus de recherche et de partage de connaissance accessibles et efficace et l'utilisation des nouvelles technologies pour l'évaluation et la compréhension de l'impact scientifique.

La Figure 1 présente la taxonomie proposée par FOSTER. Les termes prédominants sont open access, open data, open reproducible research. FOSTER définit ces termes comme suit :

- **L'open access** fait référence au libre accès des publications scientifiques, avec des restrictions de droits d'auteur et de licence limitées ou inexistantes.
- **L'open data** concerne la disponibilité des données de recherche recueillies au cours d'un projet, pour une réutilisation.
- **L'open reproducible research** est l'acte de pratiquer la science ouverte pour permettre la reproductibilité indépendante des résultats de la recherche.

Nous nous intéresserons, dans ce manuscrit, à la disponibilité des données (open data) et à la reproductibilité des résultats scientifiques (open reproducible research).

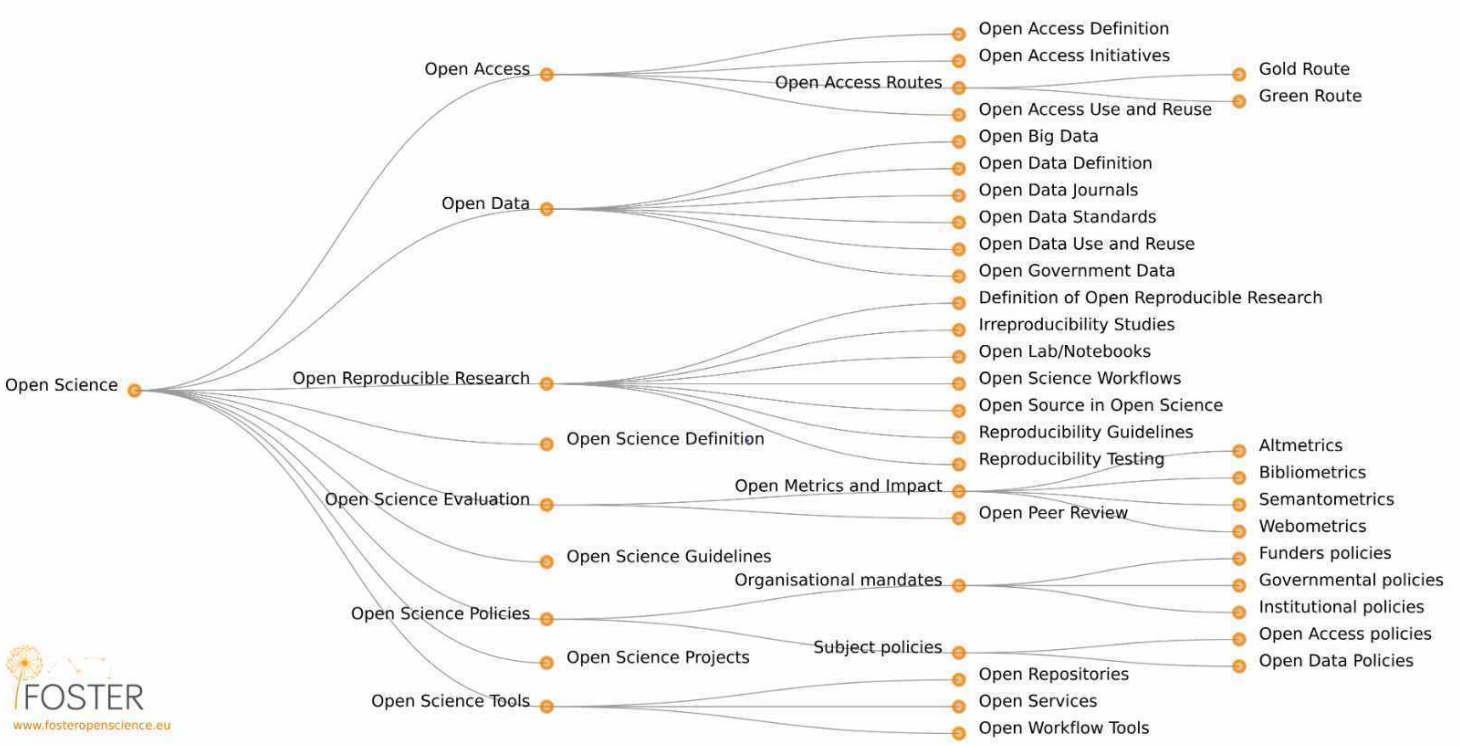

Figure 1: La taxonomie de la science ouverte.

Cette image est utilisée sous une licence CC- BY (16)

1.2. La reproductibilité : définition

La reproductibilité est l'une des conditions importantes à toute démarche scientifique. Pourtant, il n'existe pas de définition unique (17). De manière générale, la reproductibilité évoque la capacité à reproduire les mêmes résultats d'une expérience, dans les mêmes conditions. Mais que veut dire le terme « les mêmes conditions » ? Que signifie reproduire les mêmes résultats ? L'utilisation d'autres termes synonymes tels que réplicabilité ou répétabilité viennent rajouter de la confusion et faussent la compréhension de la reproductibilité.

Jon Claerbout, géophysicien à Stanford, s'intéressant aux difficultés rencontrées lors de la reconstitution d'une expérience informatique, fut l'un des premiers, en 1992, à définir la reproductibilité comme étant la capacité de recalculer à partir de toutes ses données, paramètres et programmes. [*An author attaches to every figure caption a pushbutton or a name tag usable to recalculate the figure from all its data, parameters, and programs. This provides a concrete definition of reproducibility in computationally oriented research*] (18).

Son travail a été poursuivi par d'autres chercheurs, qui y introduisent la possibilité d'expérimentateurs indépendants et la notion de réplicabilité. Répliquer signifie qu'une hypothèse scientifique est confirmé par des expérimentateurs indépendants utilisant des données, des méthodes et instruments indépendants tandis que reproduire est lorsque des enquêteurs indépendants soumettent aux données originales, leurs propres analyses et interprétations(19,20). Ces définitions des termes « répliquer» et « reproduire» se confondent avec d'autres propositions de définitions (17,21,22). Par exemple, l'Association for Computing Machinery (AMC) propose le terme « répétabilité » qui fait référence à la même équipe et au même montage expérimental [*Same team, same experimental setup*] (23).

En 2016, pour palier à toute confusion, Goodman *et al.* définissent la reproductibilité comme étant la possibilité d'obtenir les mêmes résultats ou observations, par une nouvelle analyse, utilisant les procédures que celles utilisées dans l'étude initiale. Ils proposent un nouveau lexique pour distinguer les différentes interprétations de la reproductibilité (24). Ci- dessous les définitions des trois types de reproductibilité proposées :

- **La reproductibilité des méthodes** : implique que suffisamment de détails sur les procédures et les données sont fournis pour que les analyses puissent être répétées exactement.

- **La reproductibilité des résultats** : implique que les mêmes résultats sont obtenus par une étude indépendante, utilisant des procédures aussi proches que possible de celles de l'étude originale.

- **La reproductibilité inférentielle** : implique que des conclusions similaires sont obtenus à partir d'une réanalyse de l'étude originale.

En recherche médicale, les définitions de Goodman *et al*. ont été appelées à être largement adoptées car elles évitent la confusion causée par les significations similaires des termes « reproductibilité », « réplicabilité » et « répétabilité » (17,24).

En 2021, Gundersen, Professeur au Département d'Informatique de l'Université Norvégienne des Sciences et Technologies propose une nouvelle définition de la reproductibilité en analysant un process de méthode scientifique empirique (basée sur l'expérimentation, avec l'objectif de tester une hypothèse). Selon lui, la confusion liée au terme reproductibilité ne peut être résolue qu'en comprenant et en décrivant comment nous découvrons la connaissance (25). La première partie de son analyse consiste à décrire la méthode scientifique empirique et à y identifier les concepts les plus pertinents. Il a ensuite utilisé ces concepts pour analyser la littérature existante sur la reproductibilité.

De par son analyse, Gundersen définit la reproductibilité comme étant la capacité des chercheurs indépendants à tirer les mêmes conclusions d'une expérience en suivant la documentation partagée par les chercheurs qui l'ont réalisé en premier. [*Reproducibility is the ability of independent investigators to draw the same conclusions from an experiment by following the documentation shared by the original investigators]*. Il y a alors obligation qu'une autre équipe indépendante d'expérimentateurs mène la même expérience. La répétabilité serait d'obtenir les mêmes résultats lors de la répétition d'une expérience par les mêmes enquêteurs.

Gundersen souligne que l'utilisation du terme « résultats » dans la littérature est source de confusion car cela semble signifier à la fois le résultat généré par la conduite de l'expérience et l'interprétation de l'analyse. Il apporte une solution en utilisant les termes « critère (*outcome*) »,

« analyse (*analysis*) » et « interprétation (*interpretation*) ». Les résultats peuvent être reproduits même lorsque le critère de l'expérience de reproductibilité diffère du critère de l'expérience originale, tant que l'analyse peut être interprétée de la même manière et conduire aux mêmes conclusions. De même, l'analyse peut également être différente tant que l'interprétation de l'analyse conduit à la même conclusion. Pour Gundersen, l'expérience de reproductibilité nécessite à la fois la similitude et la différence. La similitude doit être au moins la même méthodologie expérimentale. Ainsi, il identifie trois types de reproductibilité :

- **La reproductibilité du critère** :

« Le critère de l'expérience de reproductibilité est le même que le critère produit par l'expérience originale. Lorsque le critère est le même, la même analyse et la même interprétation peuvent être faites, ce qui conduit au même résultat et donc l'hypothèse est soutenue par les deux expériences » [*The outcome of the reproducibility experiment is the same as the outcome produced by the original experiment. When the outcome is the same, the same analysis and interpretation can be made, which leads to the same result and hence the hypothesis is supported by both experiments. The experiment is outcome reproducible*].

- **La reproductibilité de l'analyse** :

Ici, le critère de l'expérience de reproductibilité n'a pas à être identique au critère produit par l'expérience originale, mais tant que la même analyse peut être faite et qu'elle conduit à la même interprétation, l'expérience est dite reproductible d'analyse. [*The outcome of the reproducibility experiment does not have to be the same as the outcome produced by the original experiment, but as long as the same analysis can be made ant it leads to the same interpretation, the experiment is analysis reproducible*]

- **La reproductibilité de l'interprétation** :

Une expérience est dite reproduite d'interprétation lorsque ni le critère, ni l'analyse n'ont besoin d'être les mêmes tant que l'interprétation de l'analyse conduit à la même conclusion que celle de l'expérience originale. [*Neither the outcome nor the analysis need to be the same as long as the interpretation of the analysis leads to the same conclusion. In this case the experiment is interpretation reproducible*]

Pour finir son analyse, Gundersen identifie quatre degrés de reproductibilité en fonction des types de documents partagés par les chercheurs de l'étude primaire. La reproductibilité est donc un cas spécifique de réutilisation de résultats précédents et dépend directement de la

disponibilité de la documentation concernant l'expérience à reproduire. La reproductibilité exige alors une transparence des données comme Gundersen le souligne dans sa conclusion : « Plus il y a de documentation partagée, plus il est facile pour les chercheurs indépendants de reproduire les résultats. Plus il est facile de reproduire les résultats, plus la connaissance peut être découverte rapidement. La compréhension de la reproductibilité souligne que les progrès scientifiques rapides et réguliers exigent de la transparence [*The more documentation that is shared, the easier it is for independent researchers to reproduce the results. The easier it is to reproduce results the faster knowledge can be discovered. The understanding of reproducibility described here emphasizes that fast-paced and steady scientific progress require transparency and openness*] ».

Le concept de transparence peut être considéré comme une combinaison de pratiques liés à la reproductibilité, dont le but est de faire bénéficier les résultats de recherche à un public plus large qu'aux premiers exécutants(26).

Des pratiques et des processus de recherche transparents favorisent également l'accès aux méthodes et conclusions qui ne sont pas forcément documentées dans les publications tels que les résultats négatifs, qui ont une importance dans la conception d'études futures. Néanmoins, la reproductibilité et la transparence ne garantissent pas l'ouverture ou la disponibilité des produits de recherche (open research) et vice-versa, l'ouverture seule ne garantit pas la reproductibilité et la réutilisation (27). Des résultats peuvent être transparents et reproductibles, mais leur disponibilité peut être limitée ou sous embargo pour des questions de confidentialité par exemple. La reproductibilité et le principe de transparence sous-jacent doit aller de pair avec une plus grande ouverture des produits de la recherche, pour une science plus rigoureuse (26) (27). Une documentation complète de la démarche scientifique augmente la reproductibilité ; chacune des étapes doit être clairement rapportée en fournissant une documentation claire et raisonnablement ouverte. Pour Philip Stark, professeur au département de Statistiques à l'Université de Berkeley en Californie, fournir une description complète d'une expérience avec suffisamment de détails pour que d'autres puissent la répéter, précède la reproductibilité (28). Il le nomme le concept de « pré-productibilité [*pré-producibility*] » (28), qui englobe l'ensemble des mesures visant à garantir la reproductibilité, en documentant le processus scientifique au stade le plus précoce, avant les résultats (26).

Liz Lyon, professeure à l'Ecole des Sciences de l'information de l'Université de Pittsburg, énonce dans son article "Transparency: The Emerging Third Dimension of Open Science and Open Data", un modèle tri-dimensionnel de la science ouverte, où la transparence avec la

reproductibilité constituent la troisième dimension, les deux premières étant « Accès » et « Participation » (29). Elle y décrit un continuum d'ouverture (open) avec des organismes, des projets scientifiques et des plateformes d'infrastructure positionnés sur les axes de ces trois dimensions, selon leur degré d'ouverture (open). La dimension « Accès » concerne la capacité de localiser et d'avoir accès librement aux publications scientifiques, qu'elles soient en accès libre ou fermé. La dimension « Participation » concerne le degré de participation dans la recherche, allant d'un chercheur isolé à des équipes collaboratives jusqu'à la science citoyenne où le public non scientifique participe à la conception, la mise en œuvre et la publication de l'étude. La dimension « Transparence » concerne les pratiques et processus de recherche qui servent à faciliter et améliorer la qualité de la recherche, la confiance du public dans les conclusions découlant des activités de recherche et l'intégrité scientifique. L'intégrité scientifique, étroitement liée à la notion de reproductibilité, constitue un objectif d'action politiques des parties prenantes telles que les institutions université et de recherche, les organismes de réglementation, les sponsors publics et privés, les revues, les associations professionnelles qui soutiennent et encouragent de meilleurs pratiques de recherche, la véracité des résultats ainsi que les principes éthiques de la science et de la société (26) (30). L'intégrité scientifique « se définit comme l'ensemble des règles et valeurs qui doivent régir les activités de recherche pour en garantir le caractère honnête et scientifiquement rigoureux »(31).

Dans le chapitre 4, nous utilisons les terminologies de Goodman pour définir la reproductibilité. Pour une uniformisation des informations, nous comparons les différentes terminologies de Goodman, de Claerboot et de l'AMC dans le **tableau 1**.

Claerbout ***et al.***	**AMC**	**Goodman**	**Gundersen**
	Répétabilité		Répétabilité
Reproductibilité	Réplicabilité	Reproductibilité des méthodes	Analyse reproductible
Réplicabilité	Reproductibilité	Reproductibilité des résultats	Critère reproductible Interprétation reproductible
		Reproductibilité inférentielle	Interprétation reproductible

Tableau 1: Comparaison des terminologies en se basant sur la comparaison faite par Plesser *et al*(17).

Pourquoi la reproductibilité est un sujet incontournable en science biomédicale ? Pourquoi est-elle cruciale ?

Le 1er Mai 2020, le prestigieux journal New England Journal of Medicine (NEJM) a publié un article évaluant la relation entre les maladies cardiovasculaires, les thérapies qui y sont associées et le décès à l'hôpital chez les patients hospitalisés atteints de la Covid-19, dont les données ont été enregistrées dans Surgical Outcomes Collaborative, une vaste base de données exclusive de dossiers de santé électronique analysée par Surgisphere, une société américaine (32). Cette étude démontre que l'utilisation de ces thérapies ne présente aucun risque pour les patients.

Le 22 Mai, le journal The Lancet publie une étude, réalisée à partir de la même base de données, qui conclue que la chloroquine et l'hydroxychloroquine seraient dangereux pour les patients atteints de Covid-19 (33).

Une autre étude, publiée dans Social Science Research Network E-library, utilise également la base de données fournie par Surgisphere. Elle conclue que l'Ivermectine, médicament antiparasitaire, réduit le taux de mortalité chez les patients malades de la Covid-19.

Les conclusions de ces articles ont entrainé des retombées politiques colossales, dans un contexte tendu de crise sanitaire de la Covid-19. Pour ne citer que quelques exemples : la décision du gouvernement péruvien à ajouter l'ivermectine dans sa politique de traitement du Covid-19 ; l'annulation par décret de l'autorisation de prescription de l'hydroxychloroquine aux patients atteints de la Covid-19 ainsi que l'interruption des essais cliniques sur l'hydroxychloroquine par le gouvernement français.

Suite à la publication de ces articles, des interrogations ont commencé par surgir concernant les études elles-mêmes et la société Surgisphere (34) (35). Les données analysées se sont avérées être frauduleuses. En effet, les études portaient sur l'analyse d'un nombre incroyablement élevé de patients, qui après vérification ne correspondaient pas avec les chiffres officiels concernant les patients atteints ou décédés de la Covid-19. D'autres incohérences sur les données ont été identifiées tel que l'écart entre le faible nombre d'hôpitaux dans chaque pays ayant leurs données dans la base Surgisphere et la forte proportion de cas de Covid-19 rapportée dans les études ; une figure dans l'article sur l'ivermectine qui présentait des données différentes de celles décrites dans le texte. Dans l'étude du Lancet, la probabilité que les patients recevant les

médicaments expérimentaux soient plus malades que les témoins n'est pas contrôlée. De plus, aucun des hôpitaux recensés comme ayant contribué au registre de patients de la société Surgisphere n'a été identifié et le site de la société ne présente aucune information qui pourrait attester de ses compétences dans le domaine médical.

La question à se poser est donc comment une entreprise dont les employés n'ont aucune formation scientifique ou médicale (hormis le fondateur Sapan Desai qui est chirurgien vasculaire), peut coordonner la collecte de données de santé de patients hospitalisés, dans plusieurs pays dont les lois en matière d'éthique et de protection des données ne sont pas les mêmes ? Dans ce contexte de forte suspicion, les données ont été exigées à Sapan Desai et ses co-auteurs afin de vérifier de manière indépendante l'ensemble des conclusions. Ces dernières n'ont jamais été partagées et la majorité des co-auteurs de ces articles ont admis n'avoir pas vu les données complètes.

Le 4 Juin 2020, le Lancet et le NEJM rétractent les articles publiés.

Dans l'urgence de trouver de meilleurs moyens d'endiguer l'épidémie de Covid-19, ces études retractés ont fait perdre un temps considérable à la communauté scientifique et au monde entier qui attendaient une solution de sortie de crise sanitaire (3).

L'ouverture et la transparence du processus de recherche d'une étude augmente la possibilité de vérifier et confirmer les résultats. Les études dont les résultats ont été confirmés peuvent être directement utilisés pour d'autres recherches. Cela permet de limiter les études qui sont stoppées car elles se sont basées sur des résultats non vérifiables et de limiter les répétitions inutiles d'études, qui peuvent représenter un coût important de temps et d'argent. La reproductibilité représente alors un enjeu économique et permet de maximiser et d'assurer l'utilisation la plus efficace et efficiente des fonds de recherche (36) (37).

Le manque de reproductibilité a un impact négatif sur la confiance du public dans les conclusions scientifiques. Le manque de transparence, comme l'exemple des études rétractées citées plus haut, conduit à l'érosion de la confiance du public dans les conclusions scientifiques qui ont un impact sur leur vie. La reproductibilité et les principes associés de transparence et d'intégrité sont la solution pour démontrer la rigueur des études scientifiques et leur fiabilité et ainsi réduire les débats polémiques sur des sujets comme l'efficacité ou l'innocuité des vaccins. Même si la compréhension de la science est limitée parmi le public, ce dernier a accès à une multitude d'information grâce aux divers moyens de communication et notamment des réseaux sociaux. L'incertitude inhérente au processus scientifique peut être perçu comme un manque

de véracité par les citoyens. Le public s'attend à ce que la science fournisse des preuves fiables et veut identifier les produits scientifiques rigoureux des produits fragiles. Il est important que la manière dont sont relayés les défauts de reproductibilité ou incertitudes de la science soit fait de manière responsable, en prenant en compte la complexité du processus scientifique. Pendant la pandémie du Covid-19 par exemple, le public devenait plus méfiant quand les réponses à leurs interrogations changeaient, les hypothèses étant réduites à des résultats simplifiés de type oui ou non par les médias (38).

1.3. Crise de la reproductibilité : réalité ou abus de langage ?

Sur le récit de la crise de la reproductibilité en science, l'article du Pr Ioannidis au titre accrocheur « Why Most Published Research Findings Are False » publié en 2005, est considéré comme l'un des plus important. Ioannidis émet le postulat que la majorité des résultats de la recherche sont faux, principalement en raison de la façon dont la significativité statistique est rapportée dans la littérature. De plus, Ioannidis met l'accent sur la présence de « biais qui peuvent entrainer une manipulation dans l'analyse ou la communication des résultats » [*Bias can entail manipulation in the analysis or reporting of findings*]», sur des choix méthodologiques problématiques comme la taille de l'étude, l'existence d'intérêts d'ordre financier ou autres qui peuvent conduire à des résultats et des interprétations faussés (39).

Les tentatives échouées de reproduction d'études, et ce dans plusieurs disciplines scientifiques (40,41), font écho aux hypothèses de Ioannidis. En recherche biomédicale, la faible reproductibilité semble y être plus répandue que dans d'autres disciplines (42). Begley et Ellis rapportent dans leur article que les chercheurs du département d'hématologie et d'oncologie de la société de biotechnologie Amgen, ont tenté de confirmer les résultats de 53 études « phares » ; seules 6 des découvertes ont été confirmées avec succès (43). The Open Science Collaboration, un projet impliquant 270 scientifiques, dirigé par Brian Nosek (co-fondateur et directeur du Center of Open Science), a tenté de reproduire les effets statistiquement significatifs trouvés dans 100 études expérimentales et corrélationnelles publiées dans trois revues de psychologie de premier plan : seuls trente-six pour cent des réplications avaient des résultats significatifs (44). Plusieurs autres études de réplications ont été conduites, comme The Reproducibility project in Cancer Biology, un projet dont le but est d'étudier la reproductibilité de la recherche en biologie du cancer, en reproduisant 193 expériences à partir de 53 articles à

fort impact. Les premiers résultats montrent que seuls 50 expériences (à partir de 23 articles) ont été reproduites, le manque d'informations suffisantes sur les statistiques ou la méthodologie expérimentale étant principalement les facteurs limitants d'expériences pouvant être répétées(45).

L'idée de crise de la reproductibilité en science se répand dans la communauté scientifique, alimentée et soutenue par les critiques statistiques (39), les échecs de tentatives de reproduction (46) (47), les cas de fraudes (48) et les articles pointant du doigt les pratiques de recherche douteuses (6). Une attention accrue a été également accordée aux cas d'inconduites de recherche. En Aout 2010, deux rédacteurs scientifiques médicaux, Ivan Oransky et Adam Marcus, créaient le blog Retraction Watch, qui reporte les rétractions d'articles et les raisons du retrait. Retraction Watch a recensé un total de 500 rétractations dans la littérature scientifique en 2014 et 684 rétractions en 2015, avec une augmentation en pourcentage des rétractions en sciences biomédicales (49).

Néanmoins, l'existence de cette crise de la reproductibilité en science est niée par une partie des chercheurs. Pourtant, dans un article de Nature, l'écrivaine et éditrice scientifique Monya Baker rapportait les résultats d'une enquête, qui révèle que les résultats scientifiques sont moins reproductibles que l'on ne le pensait. Cette enquête a été réalisé sur 1576 chercheurs, qui ont répondu à un bref questionnaire sur la reproductibilité de la recherche (42) : 70% des répondants affirment ne pas avoir réussi à reproduire les expériences d'un autre scientifique et plus de la moitié n'ont pas réussi à reproduire leurs propres expériences. 52% des répondants affirment qu'il s'agit d'une importante crise de reproductibilité, 38% d'une crise légère. Seuls 3% rejettent l'existence de cette crise et 7% ont répondu qu'ils ne savent pas.

Selon Fanelli, dont les travaux de recherche portent sur la méta-recherche, l'intégrité de la science et la reproductibilité , le récit de crise qui « postule qu'une proportion importante et croissante d'études publiées dans toutes les disciplines, ne sont pas fiables en raison de la baisse de la qualité et de l'intégrité des pratiques de recherche et de publication, en grande partie à cause des pressions croissantes pour publier et d'autres maux affectant la profession scientifique contemporaine » est partiellement erroné.

[*this new "science in crisis" narrative postulates that a large and growing proportion of studies published across disciplines are unreliable due to the declining quality and integrity of research and publication practices, largely because of growing pressures to publish and other ills affecting the contemporary scientific profession*]

Il rajoute que les résultats de cette enquête non randomisée (en parlant de celle décrite dans l'article de Monya Baker) ne représentent pas la population scientifique, mais une approbation sans critique de ce « récit de crise » sur la science, divulguée par une littérature scientifique en pleine croissance, avec un nombre grandissant, depuis 2014, de publications dont le titre, le résumé ou les mots-clés, contiennent l'une des expressions suivantes : crise de reproductibilité , crise scientifique , science en crise , crise de la science , crise de réplication , crise de réplicabilité (50).

Fanelli reconnait néanmoins que la science est confrontée à des défis qui doivent être résolus mais les problèmes liés au manque de reproductibilité des résultats ne doivent pas emmener à considérer la science comme étant moins fiable. Selon Fanelli, le discours de la science « en crise » est contre-productif et « au lieu d'inspirer les jeunes générations à faire plus et mieux de la science, cela pourrait favoriser en elles le cynisme et l'indifférence. Au lieu d'inviter à un plus grand respect et à un plus grand investissement dans la recherche, cela risque de discréditer la valeur des preuves et d'alimenter des agendas antiscientifiques » [*Instead of inspiring younger generations to do more and better science, it might foster in them cynicism and indifference. Instead of inviting greater respect for and investment in research, it risks discrediting the value of evidence and feeding antiscientific agendas*]. Les discours alarmistes et négatifs entraveraient plutôt les changements positifs qu'entrainent la prise de conscience des différents manquements de la pratique scientifique. Par exemple, le nombre de rétractation croissant des articles ne doit pas être assimilé à une augmentation des pratiques frauduleuses, mais plutôt fait état de l'amélioration et de l'efficacité du système qui les détecte (51).

Allant dans le même sens que Fanelli, Jamieson part du principe que la science est la forme la plus fiable de production de connaissance et qu'elle s'auto-corrige. Les problèmes dans la pratique scientifique sont découverts par les scientifiques qui travaillent également à mettre en œuvre des solutions réactives. Le récit d'une science en crise est donc injustifié et déplacé (52). Jamieson attire l'attention des journalistes sur la façon de titrer les informations sur la non reproductibilité de la science, et appelle à éviter d'alimenter des récits dangereux qui peuvent discréditer des découvertes scientifiques. Pour Jamieson, « des récits précis peuvent accroître la compréhension du public non seulement de la nature du processus de découverte, mais aussi du caractère inévitable des faux départs et des fraudes occasionnelles. Et en faisant connaître de manière responsable à la fois les manquements à l'intégrité et les tentatives de les prévenir, les médias peuvent remplir leur fonction de responsabilité sans ébranler la confiance du public » [*accurate narratives can increase public understanding not only of the nature of the discovery*

process, but also of the inevitability of false starts and occasional fraud. And by responsibly publicizing both breaches of integrity and attempts to forestall them, news can perform its accountability function without undermining public trust…].

L'existence de la crise est rejetée plus férocement par d'autres chercheurs comme Oreskes qui affirme que « La crise est la tentative de discréditer les découvertes scientifiques qui menacent les puissants intérêts des entreprises » [*The crisis is the attempt to discredit scientific findings that threaten powerful corporate interests*] (53).

Certains chercheurs trouvent l'explication de la crise de reproductibilité dans la philosophie, histoire et sociologie des sciences. Penders et Janssens s'appuient sur les écrits philosophiques de Popper, de Kuhn et sur la sociologie de la connaissance scientifique pour démontrer que le défaut de reproduction des études fait partie, de manière appropriée, à une science informative et précieuse et ne doit pas être confondu avec une science bâclée. Ils insistent sur la distinction entre une étude bâclée, avec une méthodologie douteuse « *sloppy science* » et une étude non reproductible. Une étude bâclée a besoin d'une amélioration de la qualité des méthodes. En revanche, une étude non reproduite n'est pas nécessairement de qualité inférieure et peut offrir des opportunités d'apprendre, d'améliorer la recherche. Par conséquent, le débat ne devrait pas se focaliser sur les cas de non reproduction, mais plutôt sur la lutte contre la science dite bâclée (54) .

Concernant l'existence ou non de cette crise, il n'y a pas de réponse objective. L'enquête de Baker le révèle bien car même si 52% affirment qu'il y a une crise, une bonne partie ne considère pas la science comme étant moins fiable. Par exemple, Valentin Amrhein, va dans le même sens que Ioannidis concernant la significativité statistique, mais parle plutôt de « déclarations absurdes sur l'échec de la réplication » (55).

Il est vrai que le manque de reproductibilité dans le domaine biomédical a une portée plus grande de par l'importance des découvertes sur les populations. Même si certains considèrent qu'une science strictement reproductible ne peut exister, le progrès scientifique demandent des résultats trouvés lors des découvertes scientifiques qui persistent dans le temps, qui peuvent être vérifiés et des hypothèses réfutables par des expériences reproductibles.

De manière générale, la reproduction réussie des études, que ce soit par la même équipe (répétabilité) ou par des chercheurs externes (reproductibilité) est d'une importance fondamentale, d'où le fait que, les échecs soient considérés comme constituant une crise (56) (57) (58). Néanmoins, l'idée que les défauts de reproductibilité constituent une crise et ce à

l'échelle de la science toute entière est contestée. Que le terme « crise » soit le terme approprié ou non, le récit relatif associé a fait émerger une nouvelle spécialité, qui est la méta-recherche ou méta-science. Transdisciplinaires, les objectifs de la méta-recherche ne se limitent pas à un domaine scientifique et proposent des transformations durables en définissant des réformes à toutes les étapes de la recherche scientifique, ainsi que sa divulgation pour une science plus ouverte.

David Peterson et Aaron Panofsky, dans leur article « *Metascience as scientific social mouvement* », présentent cette spécialité en partant de son idéologie scientifique jusqu'à son avenir institutionnel et intellectuel (59). Ils définissent la méta recherche comme étant un mouvement social scientifique qui cherche à utiliser les outils de la science, en particulier la quantification et l'expérimentation - pour diagnostiquer les problèmes dans la pratique de la recherche et améliorer l'efficacité [*metascience is a scientific social movement that seeks to use the tools of science- especially, quantification and experimentation- to diagnose problems in research practice and improve efficiency*]. Ils y expliquent que la méta-recherche trouve ses origines dans trois domaines qui sont : l'activisme pour une science ouverte (open access puis open science incluant tous les produits de recherche) ; la science des sciences qui produit des études quantitatives montrant comment la science fonctionne et comment elle change avec le temps ; et les critiques statistiques et méthodologiques. Ces domaines de recherche ont trouvé cause commune avec les problèmes de reproductibilité : les critiques de la pratique scientifique ont fourni des arguments pour rendre la science plus ouverte ; les études quantitatives sur la science dépendent de masses de données, donc trouvent bénéfice dans une science plus ouverte et les chercheurs adoptent les études quantitatives démontrant le manque de qualité statistique. La crise de la reproductibilité a fourni de nouvelles opportunités pour chacun de ces domaines et ces opportunités ont été amplifiées par leurs interactions. Malgré leurs objectifs communs, ces domaines restent bien distincts. La recherche dans l'étude quantitative de la science est en partie indépendante des questions de science ouverte et d'intégrité de la recherche, les questions de science ouverte s'intéressent peu à l'intégrité de la recherche et se focalisent principalement sur la démocratisation des connaissances (**Figure 2**).

La littérature fait état d'une nécessité d'amélioration des pratiques et les études de méta-recherche, en plus de décortiquer les failles de la pratique scientifique, proposent des lignes directrices pour améliorer la reproductibilité de la recherche (36) (60) (6).

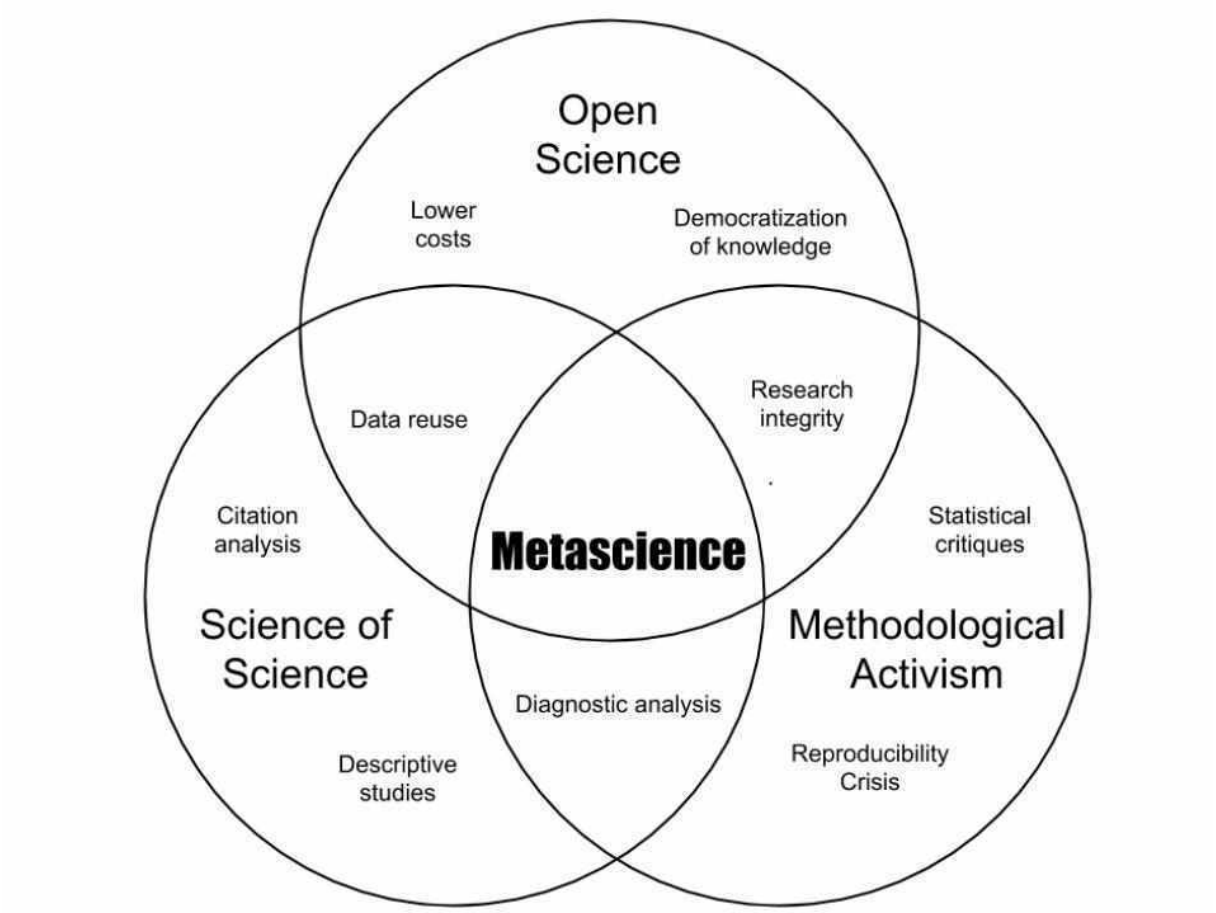

Figure 2: Les composantes de la méta-science. (Figure utilisé sans modification, sous licence CC-BY (59))

Plusieurs articles relatent les différents remèdes au défaut de reproductibilité que connait la recherche biomédicale, et plusieurs recommandations ont été faites par les acteurs impliqués pour contrer le problème. Par exemple, l'article de Munafò *et al*, intitulé « A Manifesto for Reproducible Science » énoncent des mesures à adopter, ciblant les menaces spécifiques à la science reproductible, et ce pour chaque étape de la démarche scientifique, selon le modèle hypothético-déductif (**Figure 3**). Le modèle hypothético-déductif, de façon idéal, est un modèle cyclique de raisonnement et d'observation de recherche (61), impliquant des étapes bien définies : formulation d'une hypothèse, conception de l'étude, réalisation de l'étude et collecte des données, analyse des données et interprétation et diffusion des résultats. A chacune de ces étapes peut intervenir des menaces à la validité de la recherche tels que : la mauvaise conception

des études, les mauvaises pratiques statistiques comme la faible puissance statistique et le p-hacking (formulation de l'hypothèse après connaissance des résultats), les biais de publication, la documentation inadéquate des méthodes et les problèmes de contrôle qualité (**Figure 3**). Parmi les remèdes, la promotion de la transparence et de la science ouverte avec le partage des données sont décrits comme mesures à adopter pour soutenir la vérification de la recherche et améliorer la reproductibilité dans la recherche biomédicale.

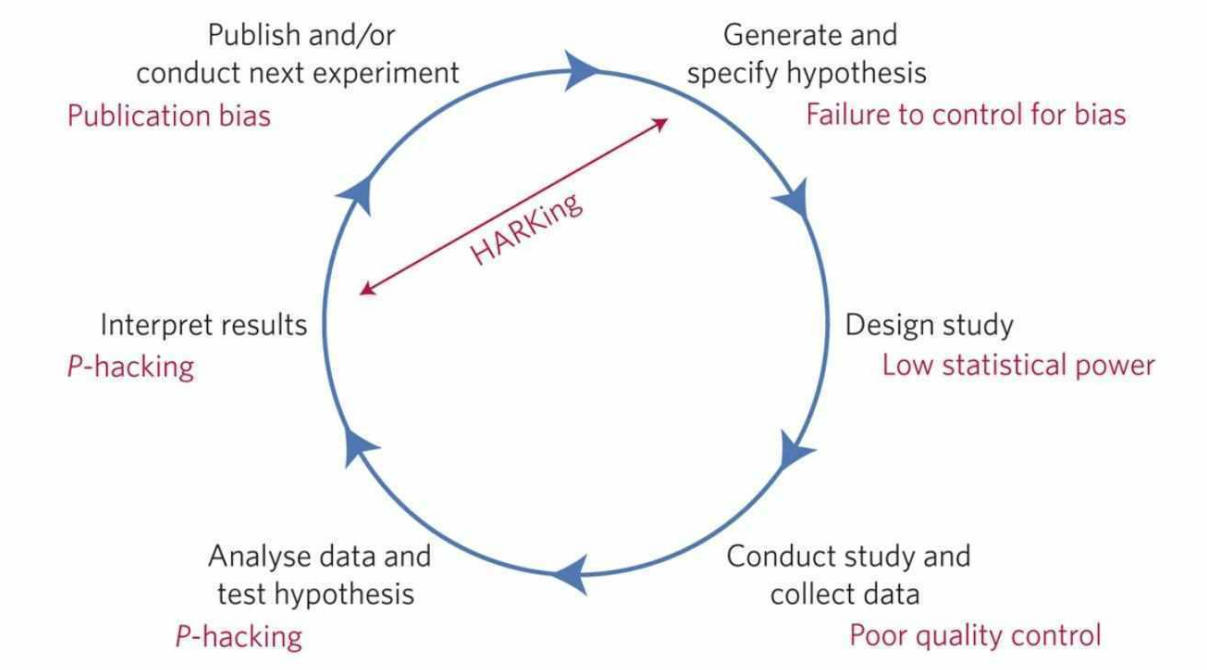

Figure 3: Modèle idéal de méthode scientifique et facteurs de défaut de reproductibilité (image utilisée sans modification, sous une Creative Commons Attribution 4.0 International License (6))

2. L'open data ou l'ouverture des données et le partage de données

L'ouverture des données, comme tout mouvement de l'open science a été poussé par l'avènement de l'internet, les avancées technologiques numériques et la multiplication des moyens d'accès à différents types de données(62). Les prémices d'ouverture de données se trouvent déjà dans la Déclaration des Droits de l'Homme et du Citoyen de 1789, qui dans son article 15, dit que « la Société a le droit de demander compte à tout agent public de son administration » (63) (64). Ceci demande donc une transparence des actions de l'Etat et l'accès à l'information publique. Cette demande n'a pas cessé d'être un impératif qui s'est concrétisée par des politiques nationales et des directives de groupes disciplinaires jusqu'à l'adoption d'une charte sur l'ouverture des données par les chefs d'Etats du G8 en 2013(65). Cette charte déclare que les données publiques des administrations des pays signataires doivent désormais être librement réutilisables par défaut. Elle reprend les principes établis lors de la conférence de Sébastopol en 2007, pendant laquelle émerge le terme « Open governement data » (66). Les personnes présentes à cette conférence, dont Lawrence Lessig, créateur des licences Creative Commons, définissent huit grands principes gouvernant les données publiques ouvertes sur la toile. Les données publiques sont reconnues comme bien public et doivent répondre aux notions d'ouverture, de participation et de collaboration. Les principes dits de Sébastopol sont à l'origine du lancement de portails à travers le monde comme data.gov aux Etats Unis en 2008, data.gov.uk au Royaume Uni en 2009 ou data.gouv.fr pour la France en 2011, donnant accès aux citoyens à des données publiques des administrations (64).

La cumulation du savoir et le potentiel économique de l'open data sont les principales raisons de l'engouement sur les questions d'ouverture de données. L'open data est considéré comme la meilleure façon de créer de la valeur ajoutée à partir du traitement de données, et permettre d' « organiser, de communiquer et de déclencher l'univers de l'intelligence collective », « de générer de la connaissance par des effets de transformation où les données sont fournies ou mises à profit dans les applications de façon innovantes » (62). La possibilité de créer de la richesse par des principes de traitement automatique des données, facilitant les réutilisations et les réinterprétations, tout en développant la transparence des administrations de l'état va entrainer la convergence des enjeux des gouvernants, des militants de la transparence et des entreprises pour faire de l'open data une des priorités de politiques numériques (62) (64).

Si les données publiques (c'est-à-dire les informations publiques produites ou reçues dans le cadre d'une mission de service public), ont été les premières concernées par une demande de libre accès, le mouvement open data s'est développé sur plusieurs scènes en parallèle, dont celui des sciences. Tout comme les données publiques, la valeur attribuée aux données issus de la recherche (67) va susciter un intérêt chez les différents acteurs du monde de la recherche, pour exploiter le maximum du potentiel des données. L'accès aux données est traduit par la possibilité de partage, en utilisant internet pour la distribution des données avec des formats utilisables sur ordinateur. Les principaux avantages du partage de données mis en avant par les parties prenantes sont la reproductibilité de la science, l'optimisation des investissements dans la recherche, la progression de la recherche et de l'innovation et la mise à disposition des ressources publiques pour la population (68). « Cette mouvance de la science ouverte et des données ouvertes suscite bien des espoirs, notamment dans la perspective d'une amélioration de la confiance dans les résultats de recherche publiés, mais aussi dans le développement de nouvelles approches de recherche et donc dans la construction de nouvelles connaissances » (69).

2.1. Initiatives internationales et nationales : impulsions à travers les organismes de financement

Les principes et lignes directrices pour l'accès aux données de la recherche financée sur fonds publics, publiés en 2007 par l'Organisation de Coopération et de Développement Economiques, OCDE, font partie des initiatives internationales majeures en matière de promotion de l'ouverture des données de la recherche. Issus d'un vaste processus de consultation, ces principes font suite à la déclaration ministérielle sur l'accès aux données de la recherche financée par des fonds publics, qui reconnait l'importance de l'accès aux données de la recherche et qui a été adoptée par les gouvernements des 30 pays membres, ainsi que ceux de l'Afrique du Sud, de la Chine, d'Israël et de la Russie. A travers cette publication, l'OCDE définit le terme *données de la recherche* et un ensemble de principes (ouverture, flexibilité, transparence, Conformité au droit, protection de la propriété intellectuelle, responsabilité formelle, professionnalisme, interopérabilité, qualité et sécurité, efficience, responsabilité de rendre compte, pérennité), pour « élaborer des politiques et bonnes pratiques en relation avec l'accessibilité, l'utilisation et la gestion des données de la recherche » (70). Elle a influencé

l'établissement des règles d'ouverture des données financées par des fonds public de plusieurs pays, ainsi que la Commission Européenne qui se sont engagées à établir des politiques conformément aux principes de l'OCDE.

De son rôle de proposer de nouveaux actes législatifs, de gérer les politiques de l'Union Européenne et d'allouer des financements européens notamment en recherche scientifique, les actions et politiques de la Commission Européenne sont également déterminants dans la promotion des pratiques d'ouverture des données de la recherche. Longtemps focalisées sur le libre accès aux publications scientifiques, la Commission Européenne commence à mettre en place, de manière progressive, des initiatives en faveur de l'ouverture des données de la recherche, impulsées par des décisions comme 1- la politique d'ouverture des données publiques (manifestée par des actions telles que la Directive 2003/98/CE dite « Directive PSI (*Public Sector Information*) concernant la réutilisation des informations du secteur public, remplacée par la Directive 2019/1024 dite « Directive Open Data » dont l'article 10 précise les conditions de réutilisation de données de la recherche financée au moyen de fonds public, ou rendues public par des chercheurs ou des organismes exerçant une activité de recherche ou finançant une activité de recherche) (71), 2- la planification des objectifs de 2020 (dont la communication intitulée « EUROPE 2020 Une stratégie pour une croissance intelligente, durable et inclusive », détaille les objectifs pour la décennie 2010-2020, avec l'initiative phare « Une Union pour l'innovation » dont l'objectif est de « de recentrer la politique de R&D et d'innovation sur les défis que notre société doit relever » à travers le cadre d'un « Espace Européen de la Recherche (EER) ») (72) et 3- la vision 2030 de l'Europe sur le développement d'e-infrastructures des données scientifiques « *Scientific Data e-Infrastructures »* dont le rapport final (publié en 2010) du groupe d'experts réuni par la Commission après 6mois d'intenses réflexions sur le sujet, soulève « l'importance cruciale de la conservation et du partage de données fiables produites au cours de la démarche scientifique » [*the critical importance of conserving and sharing reliable data produced during the scientific process*] (73).

2O12, dans une communication de la Commission présentant la phase finale de la mise en place de l'Espace Européen de la Recherche qui « est un espace de recherche unifié ouvert sur le monde, reposant sur le marché intérieur, dans lequel chercheurs, connaissances scientifiques et technologies circulent librement et grâce auquel l'Union et ses États membres renforceront leurs bases scientifiques et technologiques, ainsi que leur compétitivité et leur capacité à répondre collectivement à des défis majeurs ». L'EER doit être finalisé en 2014 et une des actions pour

se faire est d' «optimiser la diffusion et le transfert des connaissances scientifiques, ainsi que l'accès à ces connaissances », en mettant en place « un accès internet gratuit aux publications et aux données scientifiques issues de la recherche financée par des fonds publics ». La Commission invite les Etats membres à définir et coordonner leurs politiques d'accès aux informations scientifiques et de conservation ainsi que les organisations d'acteurs de la recherche à « adopter et mettre en œuvre des mesures en faveur de la liberté d'accès aux publications et données issues de la recherche financée par des fonds publics ». Concernant les données de projets de recherche financés par le programme Horizon 2020 (le programme de financement européen sur la période 2014-2020), la Commission dit développer « une méthode souple tenant compte des différents domaines scientifiques et des intérêts des entreprises » (74). Pour les projets financés par Horizon 2020, la Commission instaure une clause d'ouverture des données qui demande aux bénéficiaires un dépôt des données issues du projet de recherche financé dans une base de données de recherche (*research data repository*) et de fournir des informations suffisantes sur les outils et instruments nécessaires pour une réutilisation des données par des tiers. Initialement introduite dans le cadre du projet pilote *Open Research Data* qui n'incluait que certaines thématiques du programme Horizon 2020, cette clause a été étendue à tous les nouveaux projets du programme à partir de 2017 et s'avère ne pas être contraignante car les bénéficiaires peuvent se désengager de cette clause (opt-out) (75). La Commission tient compte des éventuels éléments qui peuvent entraver le libre accès aux données de la recherche comme la protection de la vie privée, le respect de la sécurité nationale et opte pour des données « aussi ouvert que possible aussi fermé que nécessaire ». En plus de cette clause, les bénéficiaires du programme Horizon 2020 doivent élaborer un plan de gestion de données et s'assurer que les données suivent les principes FAIR, c'est-à-dire des données faciles à trouver, accessibles, interopérables et réutilisables par l'homme et la machine (76).

Le plan de gestion de données, est un document évolutif, qui décrit les actions qui seront menées à chaque étape du cycle de vie des données (c'est-à-dire de la collection ou production, le traitement, l'analyse, la conservation, l'accès, à la réutilisation), selon un ensemble de bonnes pratiques compatibles avec les principes FAIR. Le plan de gestion permet au porteur de projet de penser en amont et de consigner le traitement des données produites ou réutilisées, de la programmation du projet, jusqu'à son achèvement. Il contient des informations sur la description des données, la documentation décrivant les données (les métadonnées), le stockage et la sauvegarde des données, les exigences éthiques et légales, le partage des données et les coûts liés à la gestion des données selon les principes FAIR. Les principes FAIR, développés

en 2016, ont été rapidement intégrés dans les politiques de partage de données. Ils « définissent les caractéristiques que les ressources de données, les outils, les vocabulaires et les infrastructures contemporains doivent présenter pour faciliter la découverte et la réutilisation par des tiers » [*The Principles define characteristics that contemporary data resources, tools, vocabularies and infrastructures should exhibit to assist discovery and reuse by third-parties*.] (77) Dans le programme Horizon Europe (2021-2027), qui prend la suite d'Horizon 2020, les exigences de science ouverte concernant l'ouverture des données restent sur la gestion des données selon les principes FAIR, avec une obligation de dépôt de données dans des entrepôts de données de référence. Nous reviendrons sur les entrepôts de données plus loin dans le manuscrit.

En France, la promotion des pratiques d'ouverture de données de la recherche est portée par le Plan National de la Science Ouverte (PNSO), lancé en 2018, qui s'inscrit dans la continuité des engagements de la Loi pour une république numérique de 2016 dont les dispositions concernant l'ouverture et la circulation des données comportaient un volet sur le libre accès aux travaux de la recherche publique. Le PNSO comporte trois axes qui sont : généraliser l'accès ouvert aux publications, structurer et ouvrir les données de la recherche, s'inscrire dans une dynamique durable, européenne et internationale. En 2021, un deuxième plan a été a annoncé et vise à généraliser les pratiques de science ouverte en France. Avec ce deuxième PNSO, la France s'aligne avec les ambitions européennes, élargit le périmètre d'ouverture aux codes sources et consolide ses actions d'ouverture de données à travers la création d'une plateforme nationale fédérée des données, Recherche Data Gouv. Cette plateforme, disponible depuis le 8 Juillet 2022, apporte aux chercheurs : un service de dépôt et de diffusion dédié aux données pour lesquelles les entrepôts disciplinaires ne sont pas adaptés, un catalogue de données de la recherche française et des services d'accompagnement. Le 29 Juin 2020, en alignement avec le PNSO et la Loi pour une République numérique, les agences de financement nationales françaises , à savoir, l'Agence nationale de la recherche (ANR), l'Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (Anses), l'Institut national du cancer (INCa), l'Agence nationale de recherches sur le sida et les hépatites virales (Inserm/ANRS) et l'Agence de la transition écologique (Ademe), ont signé une déclaration conjointe en faveur de la science ouverte. Cette déclaration est issue d'une volonté de constituer un réseau d'échange et de mettre en place des actions en faveur de la science ouverte de manière concertée. Par cette déclaration, ces agences de financement s'engagent à favoriser l'ouverture des données de la recherche en suivant le principe « aussi ouvert que possible aussi fermé que nécessaire » et

demandent aux bénéficiaires, l'élaboration d'un plan de gestion de données dès le démarrage du projet financé (78). A travers ces actions, la France s'engage sur la voie de l'ouverture des données de recherche, quoi que tardivement par rapport à d'autres pays, qui par l'engouement de leur agence de financement, ont une longueur d'avance.

Au Royaume Uni, la *Natural Environment Research Council, NERC* a mis en place une politique d'accès aux données dès 1996, puis à partir de 2005, des agences de financement comme *The Medical Research Council, Biological and Biomedical Sciences Research Council,* Wellcome. Mais ce n'est qu'à partir de 2007 que le développement des politiques d'accès aux données de la recherche prend de l'élan sous l'influence des principes et lignes directrices de l'OCDE. S'en suit une poussée vers l'harmonisation des politiques, favorisant la cohérence des recommandations pour faire progresser les pratiques de gestion et de partage des données (79).

Aux Etats Unis, en 2013, l'*Office of science and technology policy,* de *l'Executive Office* du Président, charge chaque agence fédérale avec plus de 100 millions de dollars en dépenses annuelles consacrés au financement de la recherche et du développement, de mettre en place le *Agency Public Access Plan,* pour soutenir un meilleur accès de la communauté scientifique, de l'industrie et du public aux résultats de la recherche financée par le gouvernement fédéral. En plus de la mise à disponibilité en libre accès des articles scientifiques dans les douze mois suivant leur publication, les données issues de projet de recherche non classifié, financé partiellement ou intégralement par fond fédéral doivent être stockées, accessibles au public dans le but d'être réutilisées (80) . Chaque plan doit porter sur des aspects précis dont la promotion du dépôt de données dans des bases de données ouvertes (« *publicly accessible databases* ») et l'obligation des chercheurs recevant des financements fédéraux à élaborer des plans de gestion de données. Ces recommandations s'alignent avec plusieurs initiatives comme l'élaboration d'une politique de partage de données par la *National Science Foundation* (NSF) en 2010 et l'obligation des bénéficiaires à rédiger un plan de gestion de donnée, décrivant la conformité de la proposition de recherche à la politique de la NSF sur le partage des donnée (81).

On peut résumer l'action des financeurs de la recherche pour promouvoir l'ouverture et le partage des données à un ensemble de recommandations et d'exigences aux bonnes pratiques de gestion de données en encourageant leur partage. Cela est aussi vrai pour ceux qui financent la recherche clinique. La crise de la reproductibilité ayant eu un écho important dans la discipline, les urgences de santé qui nécessitaient la mise en commun des connaissances pour trouver des solutions, ont poussés à inclure dans les politiques de partage, les données issues d'essais cliniques qui étaient jusque-là confidentiels. Des actions comme les déclarations

conjointes des agences et institutions de financements en faveur d'un partage de données issues de la recherche biomédicale, complètent les initiatives de transparence dont l'obligation d'enregistrement des essais dans des registres dédiées et l'ouverture des résultats quel que soit la conclusion. Robert Kiley *et al*, dans un article publié dans le NEJM, relate le point de vue des financeurs des essais cliniques sur le partage des données, plus précisément celui du Wellcome Trust, The Medical Research Council, Cancer Research UK et Bill and Melinda Gates Foundation qui partagent la même perspective. Selon Kiley, le potentiel de la réutilisation des données lors de l'épidémie d'Ebola débuté en 2004 a confirmé l'importance du partage pour ces financeurs qui ont mis en place des politiques de partage de données stipulant que les données des études financées, y compris les essais cliniques, doivent être mises à disposition d'autres chercheurs au moment de la publication (82).

Le partage des données issues d'essais clinique relève également d'une obligation éthique (83). Tirer le plus grand bénéfice de données existantes pour faire avancer la science et améliorer les soins permet de limiter les essais cliniques. Plus particulièrement ceux conduisent à une mise en danger des participants. Le partage de données issues d'essais cliniques concerne plus précisément les ensembles de données individuelles des patients (*Individual Patient Data*, *IPD*) et autres produits issus de l'essai comme le protocole, les rapports d'études cliniques, les plans d'analyse statistique, les formulaires de consentement vierges.

L'industrie pharmaceutique, qui joue un rôle essentiel dans le financement de la recherche nécessaire au développement de nouveaux médicaments (84) a également déployé des actions considérables pour ouvrir les données issues des essais cliniques qu'elle finance. Les compagnies pharmaceutiques se sont dotées de politiques de partage de données et soutiennent la création de plateformes de partage où les données individuelles de patients et autres documents d'essais fiancés par l'industrie sont accessibles aux scientifiques sous certaines conditions (85). Ces plateformes hébergent également les données d'essais financés par la recherche académique mais celle-ci sont peu nombreuses à y être présentes.

2.2. Impulsions éditoriales

Les éditeurs de revues scientifiques sont des acteurs importants dans le processus de diffusion des activités de recherche. Principalement concernés par l'accès libre aux publications scientifiques, ils ne sont pas en reste concernant l'ouverture des données de recherche, plus précisément les données liées aux publications. Des revues se sont dotées de politiques de données, afin de promouvoir le partage et la réutilisation des données sur lesquelles reposent les conclusions publiées. Des recherches antérieures sur les politiques de partage de données, déclarées par les revues montrent une augmentation de la prévalence des politiques de données, allant de 15% (résultats d'une étude de 1995 examinant 850 revues) à environ 50% (résultats d'une étude de 2015 examinant 370 revues) (86). Une analyse des politiques éditoriales en 2019, montrait qu'environ 77% des revues les plus citées en physique, neurosciences et recherche opérationnelle avaient intégré une politique de données de recherche dans leurs processus éditoriaux (87). Sun Huh, rédacteur en chef de l'éthique de *Archives of Plastic Surgery* attribue l'accélération de l'adoption des politiques de partage de données par les revues à la publication de la troisième version des « Principes de transparence et de meilleures pratiques dans l'édition savante » (88). Rédigés par le Comité d'éthique de la publication (*Committee on Publication Ethics*), le Directory of Open Access Journals (DOAJ), l'Association des éditeurs universitaires en libre accès (*Open Access Scholarly Publishers Association*) et l'Association mondiale des rédacteurs médicaux (*World Association of Medical Editors*), ces principes précisent que les politiques sur le partage et la reproductibilité des données doivent être clairement énoncées dans l'éthique de publication des revues. Cette précision signifie simplement que l'éditeur doit annoncer les politiques de la revue sur le partage de données et la reproductibilité sans en faire une obligation. Les politiques de données des revues ont alors tendance à varier. Tout comme les financeurs, les politiques des éditeurs de revues décrivent comment, quand et où les données doivent être publiées. Cela mène à des politiques de partages variables entre recommandations et obligations aux auteurs. Une analyse des politiques de données de 150 revues issus de 15 disciplines (regroupées en 5 groupes disciplinaires à savoir les sciences biomédicales, les sciences physiques, les sciences sociales, l'art et les sciences humaines, sciences formelles) révèle que seuls 69 ont une politique de partage de données, dont 20 exige le dépôt préalable de certains types de données comme condition à la publication (86). Cette analyse confirme également l'avance des sciences biomédicales comparé aux autres disciplines, avec plus de 50% des revues possédant une

politique de partage de données. En regardant de plus près, les politiques de données en sciences biomédicales ont moins tendance à exiger le partage de données et que plus la recherche est orientée vers des fins médicales, moins elle est partagée. L'analyse souligne également la confusion lorsque les politiques de partage font mention d'enregistrement des essais cliniques dans des registres qui ne permettent pas l'accès aux données. En retirant l'enregistrement des essais cliniques comme exigence d'ouverture et de partage de données, seules 30% des revues biomédicales ont une politique de partage de données.

L'exigence de déclaration de disponibilité des données est un moyen d'informer sur l'accessibilité. Cette exigence est une action notable des revues pour un accès effectif aux données dans un but de réutilisation. En 2016, *l'*ICMJE *International Committee of Medical Journal Editors* un groupe de revues médicales, a annoncé vouloir exiger des chercheurs, que les données individuelles anonymisées des patients soient rendues publiques au plus tard six mois après la publication des résultats de l'essai. En 2017, l'ICMJE est revenu sur sa décision en recommandant juste un plan de partage à inclure dans chaque article, au lieu de l'obligation de partage(89). Ce plan de partage doit être également spécifié dans l'enregistrement préalable de l'essai clinique dans les registres adéquats.

Bien avant les recommandations de l'ICMJE, la revue médicale *Annal Internal of Medicine* fut la première à encourager le partage des données en 2007, suivi par la revue BMJ *British Medical Journal* qui fait la même recommandation en 2009 qui devient par la suite obligatoire pour les essais cliniques en 2013 et pour toutes les recherches en 2015. Le groupe BioMed Central proposait en 2013, que les données des articles publiés en libre accès, et les fichiers supplémentaires, soient disponibles sous la licence Creative Commons CC0, plutôt que CC-BY, faisant tomber les données dans le domaine public(90).

Outre les politiques de données, de nouvelles offres éditoriales voient le jour, dans le but de faciliter la découverte et l'accès aux données de la recherche. Un des exemples est le *data paper* ou article de données dont l'objectif est de mettre au même niveau que les publications de résultats, celle des données. Un *data paper* décrit un ensemble des jeux de données, avec toutes les informations nécessaires, pour son utilisation future. Il est préconisé de le publier avant les résultats, afin de faciliter l'évaluation de la qualité des données avant analyse (91). Les jeux de données décrits dans le *data paper* sont déposés dans un entrepôt de données, et sont reliés à l'article par un identifiant pérenne.

Le *registered report* est un autre format de publication, qui n'est certes pas centré sur la diffusion des données, mais est pensé pour améliorer la transparence de la recherche. Le principe du *registered report* est le suivant : les auteurs rédigent le protocole de leur recherche qu'ils soumettent à la revue, qui la fait évaluer par des pairs, comme dans le cas d'une soumission normale d'un article. Après évaluation par les pairs, si accepté, les auteurs commencent la collecte des données et l'analyse conformément à la méthodologie détaillée dans le protocole. La deuxième étape constitue en la soumission de l'article proprement dit, évalué à son tour par les pairs. Le rejet de l'article n'étant possible que s'il y a des changements trop importants et non expliqués dans la méthodologie initialement évaluée. Ce type de publication met en avant l'importance de la qualité de la méthode et de la question de recherche. Il permet aussi de lutter contre les mauvaises pratiques de recherche telles que les biais de publication, la sélection des résultats (publication des résultats positifs uniquement) ou la faible puissance statistique. Nous utilisons cette méthode de publication dans le chapitre 4 où nous discuterons des limites qu'elle peut avoir dans le cadre d'un projet de thèse (92).

Nous pouvons également citer l'initiative développée par le *Center of Open Science* intitulée les TOP guidelines (*Transparency and Openess Promotion guidelines*). Les TOP guidelines regroupent huit normes de transparence, chacune avec trois niveaux de rigueur croissante qui résument les pratiques à adopter pour améliorer la transparence et la reproductibilité de la recherche. Ces niveaux sont conçus pour aider les revues et les financeurs à améliorer leurs politiques. Le TOP factor, basé sur les TOP guidelines, a été conçu comme alternative au système d'évaluation de la qualité des revues porté par l'*Impact factor,* pour évaluer les politiques des revues en fonction de leur conformité aux TOP guidelines. Le TOP factor « évalue les politiques des revues pour déterminer dans quelle mesure elles promeuvent les normes savantes fondamentales de transparence et de reproductibilité » [*assesses journal policies for the degree to which they promote core scholarly norms of transparency and reproducibility]* (93).

Les alternatives comme le TOP factor montrent la volonté d'améliorer la pratique scientifique en intégrant les pratiques de données ouvertes (de science ouverte en général) dans l'évaluation de la qualité de la recherche que ce soit le système de diffusion de la recherche (donc le système éditorialiste) ou le système d'évaluation de ceux qui pratiquent la recherche pour leur recrutement dans les institutions de recherche ou l'octroi d'un financement. Comme on peut le lire sur le site du *Center of Open Science,* le « TOP Factor complète d'autres efforts visant à améliorer la culture et la pratique de la recherche. La déclaration d'évaluation de la recherche

(DORA) stipule que la recherche doit être évaluée sur ses propres mérites, et non sur la revue dans laquelle elle est publiée. TOP Factor aide à concrétiser la vision de DORA. Les auteurs peuvent utiliser TOP Factor pour identifier les revues qui ont des politiques alignées sur leurs valeurs et créditer leurs efforts pour être plus rigoureux et transparents. Les bailleurs de fonds peuvent utiliser TOP Factor pour évaluer quelles revues sont les plus susceptibles de soutenir leurs mandats politiques pour les bénéficiaires. De plus, les éditeurs peuvent utiliser TOP Factor pour identifier les revues avec des politiques progressistes pour s'inspirer et surveiller les tendances des politiques par discipline. » [*TOP Factor complements other efforts to improve research culture and practice. The Declaration of Research Assessment (DORA) states the research should be evaluated on its own merits, not the journal in which it is published. TOP Factor helps realize the DORA vision. Authors can use TOP Factor to identify journals that have policies aligned with their values and credit their effort to be more rigorous and transparent. Funders can use TOP Factor to assess which journals are most likely to support their policy mandates for grantees. And, publishers can use TOP Factor to identify journals with progressive policies for inspiration, and monitor trends in policies by discipline*] (93).

Pour revenir sur la déclaration d'évaluation de la recherche DORA, elle est un ensemble de recommandations, mis au point par un groupe de rédacteurs en chef et éditeurs de revues, réuni le 16 Décembre dans le cadre du congrès de l*'American Society for Cell Biology* (ASCB). Elle défend une évaluation de la recherche basée sur des critères autre que les indicateurs de publications classiques dont les insuffisances en tant qu'outil d'évaluation ont été démontré (94)et sont la cause de mauvaises pratiques comme le Publih or Perish qui poussent les chercheurs à publier toujours plus, ce qui emmène à des dérives (publications de résultats partielles ou publication multiple de même résultats, textes factuels, méthodologie peu approfondies) entrainant une baisse de la qualité des publications et des résultats peu reproductibles. Elle promeut la reconnaissance des données au même titre que les publications, et la valorisation des pratiques de science ouverte améliorant d'intégrité, de transparence et la reproductibilité de la science. Elle précède les Principes de Hong Kong, établis en 2019 lors de la sixième conférence mondiale sur l'intégrité scientifique, sur la promotion de l'intégrité de la recherche dans l'évaluation des chercheurs. Les principes de Hong Kong défendent la reconnaissance et la récompense des pratiques renforçant l'intégrité de la recherche (95).

2.3. Les infrastructures d'information : les entrepôts de données

Les entrepôts de données ou *data repositories* occupent une place importante dans les politiques d'ouverture de données et facilitent le stockage, l'archivage et le partage de données. Ce sont des « services en ligne permettant la collecte, la description, la conservation, la recherche et la diffusion des jeux de données » (96). Ce sont des outils majeurs « qui à la fois viennent soutenir la gestion des données de recherche et rendent possibles la transparence des travaux de recherche, comme la réutilisation de leurs données. Elles permettent de tracer ces données grâce à des métadonnées descriptives, de les rendre accessibles au public ou à des groupes d'utilisateurs sélectionnés (par exemple, en raison d'une protection juridique des données personnelles), tout comme d'assurer leur conservation à long terme. »(97) Il existe plusieurs catégories d'entrepôts de données, en fonction des disciplines scientifiques, de la gouvernance ou du type de format de données. On distingue alors des entrepôts disciplinaires, institutionnelles ou génériques. Les entrepôts de données contribuent aux principes FAIR et participent à « la reconnaissance des données de recherche en tant qu'objets d'information en soi dans la communication scientifique » (97). Les données peuvent être citées en leur attribuant un identifiant pérenne comme le *Digital Object Identifier* (DOI). Avec cet identifiant pérenne, les données peuvent être reliées à d'autres résultats de travaux de recherche, permettant de faire le lien publication et données, et d'assurer la visibilité des produits de recherche.

Les politiques de données des financeurs par exemple, soutiennent, financent et mettent l'accent sur l'utilisation des entrepôts de confiance pour stocker et rendre disponible les données de la recherche. Avec la multiplicité des offres, il est essentiel que l'entrepôt respecte des critères qui permettent de répondre aux questions de confidentialité, d'éthique et au besoin de transparence et de réutilisation. Il est aussi important d'identifier l'entrepôt qui correspond le mieux pour stocker et archiver ses données de recherche. Plusieurs solutions existent comme la plateforme re3data qui est un registre mondial d'entrepôts de données, tenu par l'Université Humboldt de Berlin, le Centre de recherche allemand GFZ pour les géosciences, l'Institut de technologie de Karlsruhe (KIT) et l'Université Purdue, qui permet de faire une recherche filtrée sur des informations comme la discipline, le type de licences d'accès, les modalités d'accès aux données et à l'entrepôt, les certifications de confiance.

L'accès aux données, le partage des données et la réutilisation ne peuvent être possible que s'il existe des outils et ressources disponibles et compatibles à la complexité des données de

recherche. En recherche clinique, les plateformes de données permettent de maitriser les risques liés au partage et apportent des solutions aux défis qui peuvent être des freins à faire du partage de données une norme (98). On peut citer la garantie de données correctement préparés et disponibles à plus long terme, stockés en toute sécurité et soumis à une gouvernance rigoureuse, la protection des participants, l'interopérabilité des données, l'accès contrôlé des données.

3. Les objectifs de la thèse

3.1. Le projet ReITheR

« Reproducibility in Therapeutic Research », dit ReITher, est un projet de méta-recherche, financé par l'Agence Nationale de la Recherche (ANR). ReITheR s'inscrit dans le contexte de l'intérêt croissant du partage de données en médecine et se veut :

- D'explorer l'ampleur de la « crise » de reproductibilité en médecine
- De mieux informer les éditeurs, les bailleurs de fonds et les autres parties prenantes sur la question de savoir si leurs nouvelles politiques concernant le partage de données fait de la science une science meilleure, plus transparente et reproductible.

ReITher comprend une série de tâches distinctes, interdépendantes et réparties en deux projets de thèse.

Le premier projet de thèse explore dans un premier temps la mise en place et l'adoption des politiques de partage de données dans les revues biomédicales qui suivent les directives de l'ICMJE. L'impact des initiatives du partage de données en termes d'intention réelle de partager et de réutilisation a été aussi exploré. Le second volet de la thèse explore la reproductibilité des essais cliniques ayant conduit à une autorisation de mise sur le marché au sein de l'Union européenne.

Les travaux du second projet de thèse seront développés dans ce manuscrit.

3.2. Notre thèse

Le point de départ des axes développées dans cette thèse était l'évaluation de l'accessibilité aux données, depuis que faire du partage de données issues des essais cliniques la norme est devenu le cheval de bataille de toutes les parties prenantes, voulant rendre la recherche biomédicale plus transparente. Faire du partage des données une norme et une réalité n'est pas sans difficultés et doit être encadré pour en tirer le meilleur. Ceci est d'autant plus vrai en recherche clinique, où le partage de données devient une question d'éthique en prenant en compte la mise en danger des patients participants aux essais (99) (100). Il est alors nécessaire d'évaluer les initiatives pour le partage des données et leurs promesses en matière de transparence, de reproductibilité, d'éthique et de maximisation.

L'étude de Naudet *et al*, a servi d'étude préliminaire pour poser les objectifs de cette thèse (101). Cette étude explorait la disponibilité des données, la faisabilité et la précision des réanalyses réalisés à partir d'essais cliniques randomisés publiés dans les revues BMJ et le Plos Medicine, revues qui avaient déjà une politique de partage de données avant les recommandations de l'ICMJE en 2016.

Partie 1 :

L'objectif de cette première partie est de fournir un aperçu de la disponibilité des données des essais cliniques.

Les résultats de l'étude de Naudet et *al*, publiés en 2018, montraient que malgré les politiques de partage de données fortes du BMJ et de Plos Medicine, la disponibilité des données n'était pas optimale.

Plusieurs audits, ont montré l'étendue de la mise en place des politiques de partage au sein des financeurs. La mise en pratique de nouvelles méthodes évolue et les audits ont été réalisés sur un nombre sélectionné de financeurs. (102) (103) (104)

Dans le Chapitre 2, nous mettons à jour les conclusions de ces audits, en se basant sur deux grands échantillons représentatifs de financeurs commerciaux et non commerciaux internationaux. Pour se faire, nous avons évalué le pourcentage de bailleurs de fonds ayant une politique de partage de données et décrit ces politiques. Pour finir, nous avons évalué la conformité des ECR financés avec les politiques de partage de données existantes en termes d'intention de partager des données.

Dans un second temps, nous étendons notre analyse sur les financeurs des essais clinique en France pour fournir un état des lieux de la mise en place de politiques de partage de données par les financeurs d'essais cliniques.

Partie 2 :

L'établissement des politiques de partage de données garantit il le partage réel des données ? Les pratiques actuelles correspondent-elles aux recommandations de partage de données ? Comment réduire les écarts entre les politiques et leur mise en œuvre ?

Dans le Chapitre 3, nous apportons des éléments de réponses à ces questions, en s'appuyant sur les conclusions d'études réalisés dans le cadre du projet Reither, dont l'objectif était l'évaluation des politiques de partage en place et leur application réelle.

Dans les deux premières parties de la thèse, nous questionnons essentiellement le rôle des financeurs, dans le passage de la mise en place d'une politique de partage de données à une pratique effective, scientifique, reproductible avec des données disponibles et accessibles.

Partie 3 :

Naudet *et al* suggéraient également que les changements dans les conclusions suite à une nouvelle analyse ne sont pas aussi fréquents qu'on le pensait. Lorsque les chercheurs partagent leurs données, les réanalyses ont largement reproduit les résultats originaux. Ils concluaient aussi que les pratiques de partage de données doivent se généraliser et être simplifiées pour permettre des réanalyses et une réutilisation significative des données.

Les efforts en matière d'ouverture des données ont conduit à la création de plateforme de partage (105). Ces plateformes de partage de données permettent un accès sécurisé aux données, répondant aux inquiétudes de protection des données des patients. Malgré la disponibilité des essais sur ces plateformes, très peu des réutilisations publiées sont des réanalyses dont une minorité exécutée par des équipes indépendantes (5).

Dans le Chapitre 4, nous nous intéressons à la transparence des essais cliniques et au processus de demande de données sur les plateformes de partage de données.

L'objectif principal de notre étude est d'évaluer la reproductibilité de la recherche thérapeutique ; en réanalysant un large éventail de données d'essais cliniques disponibles sur

des plateformes de partage. Nous utilisons la méthode de publication du Registered report pour cette analyse.

CHAPITRE 2 : Les politiques de partage de données des financeurs en recherche thérapeutique

1. Les financeurs commerciaux et non commerciaux

Funders' data-sharing policies in therapeutic research: an audit of commercial and non-commercial funders

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Jeanne Gaba a participé à la conception de l'étude (design, rédaction du protocole), à l'extraction des données, à l'analyse des données, à l'interprétation des résultats et à la rédaction de l'article.

RESUME

Contexte

Les financeurs sont des acteurs clés dans la promotion du partage des données issues d'essais contrôlés randomisés (ECR). Cette étude a pour objectif de décrire les politiques de partage de données des financeurs commerciaux (compagnies pharmaceutiques) et non commerciaux et d'évaluer la conformité des ECR financés avec les politiques de partage de données existantes.

Méthodes et résultats

Nous nous sommes intéressés aux organismes de la recherche clinique ayant financé au moins un ECR dans les années 2016 à 2018. 78 financeurs non commerciaux éligibles extraits du site Web de Sherpa/Juliet Initiative et un échantillon aléatoire de 100 financeurs commerciaux sélectionnés parmi les listes de membres d'associations pharmaceutiques (LEEM, IFPMA, EFPIA) et les 100 premières entreprises pharmaceutiques en termes de ventes de médicaments ont été inclus.

Trente (sur 78 ; 38 %) financeurs non commerciaux avaient une politique de partage de données, dix-huit (sur 30, 60 %) rendant le partage de données obligatoire et douze (40 %) encourageant le partage de données. Quarante et un (sur 100 ; 41 %) des financeurs commerciaux avaient une politique de partage des données.

Deux échantillons aléatoires de 100 ECR enregistrés sur Clinicaltrial.gov, dont les financeurs ont été précédemment identifié comme ayant une politique de partage ont été inclus. Des déclarations de partage de données étaient présentes pour soixante-dix-sept (77 %, 95 % IC [67 % -84 %]) et quatre-vingt-un (81 % [72 % - 88 %]) des ECR financés respectivement par des financeurs non commerciaux et commerciaux. L'intention de partager les données a été exprimée dans 12 % [7 % - 20 %] et 59 % [49 % - 69 %] des ECR financés par des financeurs non commerciaux et commerciaux, respectivement.

Conclusion

Cette étude a identifié des performances sous-optimales des bailleurs de fonds dans la mise en place de politiques de partage de données. Pour ceux qui avaient une politique de partage de données, la mise en œuvre de la politique dans l'enregistrement des ECR était limitée pour les financeurs commerciaux et préoccupante pour les financeurs non commerciaux. Les limites de la présente étude incluent sa nature transversale, puisque les politiques de partage des données sont en constante évolution. Nous appelons à une normalisation des politiques avec une forte composante d'évaluation pour s'assurer que, lorsqu'elles sont en place, ces politiques sont efficaces.

ABSTRACT

Background

Funders are key players in supporting randomized controlled trial (RCT) data-sharing. This research aimed to describe commercial and non-commercial funders' data-sharing policies and to assess the compliance of funded RCTs with the existing data-sharing policies.

Methods and findings

Funders of clinical research having funded at least one RCT in the years 2016 to 2018 were surveyed. All 78 eligible non-commercial funders retrieved from the Sherpa/Juliet Initiative website and a random sample of 100 commercial funders selected from pharmaceutical association member lists (LEEM, IFPMA, EFPIA) and the top 100 pharmaceutical companies in terms of drug sales were included.

Thirty (out of 78; 38%) non-commercial funders had a data-sharing policy with eighteen (out of 30, 60%) making data-sharing mandatory and twelve (40%) encouraging data-sharing. Forty-one (out of 100; 41%) of commercial funders had a data-sharing policy.

Among funders with a data-sharing policy, a survey of two random samples of 100 RCTs registered on Clinicaltrial.gov, data-sharing statements were present for seventy-seven (77%, 95% IC [67%-84%]) and eighty-one (81% [72% - 88%]) of RCTs funded by non-commercial and commercial funders respectively. Intention to share data was expressed in 12% [7%-20%] and 59% [49% – 69%] of RCTs funded by non-commercial and commercial funders respectively

Conclusions

This survey identified suboptimal performances of funders in setting up data-sharing policies. For those with a data-sharing policy, the implementation of the policy in study registration was limited for commercial funders and of concern for non-commercial funders. The limitations of the present study include its cross-sectional nature, since data-sharing policies are continuously changing. We call for a standardization of policies with a strong evaluation component to make sure that, when in place, these policies are effective.

INTRODUCTION

Ensuring that the science they fund meets the highest research integrity standards is a key issue for funders involved in clinical research. According to the International Committee of Medical Journal Editors (ICMJE), an influential working group of general medical journal editors, trial data-sharing is an ethical imperative (106) and should therefore be one of their priorities. Data-sharing aims to maximize the benefits that can arise from individual patient data (IPD) by exploring new or unresolved issues from completed trials, by pooling them in large IPD meta-analyses or by re-analyzing the initial trial data (106). It also ensures "transparency, openness, and reproducibility" (107) and evaluates the risk taken by patients participating in clinical trials.

The G7 clearly calls for open practices in science as one of their top priorities (108) and various calls to action from clinical research stakeholders to data generators, such as pharmaceutical companies, universities, charities, regulatory agencies, have led to the implementation of policies and recommendations to responsibly share clinical trial data (82). Data-sharing platforms such as Clinical Study Data Request, the Yale University Open Data Access (YODA) Project and Vivli were created to facilitate data-sharing and to ensure that clinical trial data are FAIR (Findable, Accessible, Interoperable and Reusable) (76). The ICMJE has promoted data-sharing by requiring authors to include a data-sharing statement in published articles and to register a data-sharing plan for any new trial (109). However, to be effective, these initiatives need to be supported by funders, as they require dedicated resources for data-sharing plans of this nature. Data-sharing is not a panacea; it entails considerable challenges, such as privacy and patient consent, and it implies substantial costs for the preparation of the data (110).

Funders are therefore key players in supporting data-sharing and are expected to provide appropriate guidance and to require best practice from their grant recipients(82). However, funder policies and attitudes toward data-sharing have rarely been explored. Concerning commercial funders, a prior survey of 23 top pharmaceutical companies in 2016 found that almost all of them (22; 96%) had a policy to share IPD. The proportion was 71 % among a less selected sample. The policies were however different (111) and lower proportions were found in a 2019 survey with only 25 % of large companies making IPD accessible, a proportion that was slightly improved after communication and feedback to the firms (112). Concerning non-commercial funders, a 2017 survey on 20 non-commercial funders of health research found that 10 had a data-sharing policy with only 2 requiring IPD sharing (113).

We designed this survey to update the previous ones on two large, representative samples of international commercial and noncommercial funders, and to explore the implementation of funders' data-sharing policies. The aims of this research were to evaluate the percentage of funders with a data-sharing policy, to describe these policies and to assess the compliance of funded RCTs with the existing data-sharing policies in terms of intention to share data.

METHODS

A protocol was registered before the start of the research on the Open Science Framework (OSF) (https://osf.io/mkxzf/). This study was divided into two parts: a survey of funder data-sharing policies and a survey of registered RCTs.

All outcomes were reported and described by numbers, percentages and, where appropriate, the corresponding 95 % confidence intervals were presented. Verbatim quotes from funder policies were presented qualitatively using examples, word clouds and a detailed list.

For all random samples, we estimated that a random sample of 100 (funders and/or studies) was sufficient to estimate a percentage of 50 % (the worst scenario for precision estimates) with a precision (boundaries of the 95 percent confidence interval) of +/- 9.8 %.

All analyses were performed with R version 3.4.1.

Survey of funders' data-sharing policies

Eligibility criteria and search strategy to identify funders

We included funders of clinical research with at least one RCT funded (regardless the design, the population, the intervention or the outcomes) in the course of the years 2016 to 2018, and with an accessible website in English.

We searched for non-commercial and commercial funders. Non-commercial funders were retrieved on the Sherpa/Juliet Initiative website (114). SHERPA/Juliet is a searchable database providing information on non-commercial funders' policies, especially concerning open access. Commercial funders were selected from different lists of pharmaceutical industry associations: the European Federation of Pharmaceutical Industries and Associations (EFPIA)(115), the Pharmaceutical Research and Manufacturers of America (PhRMA)(116), the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) (117) and "Les Entreprises du Médicament" (LEEM, a professional organization of pharmaceutical companies operating in France)(118). We added the list of the top 100 pharmaceutical companies in terms of drug sales in 2016 (119) which was not planned in the first draft of our protocol.

Funder selection and data extraction

A data extraction sheet was developed from a test sample of ten funders that exhibited feasibility of outcome extraction. Two authors (JG, MS) independently performed the eligibility assessment and extracted information from funders' websites. Disagreements were resolved by consensus and a third author (FN) was consulted in case of disagreement.

Outcomes describing funders' data-sharing policies

The primary outcome for this survey was the existence of a data-sharing policy (i.e. clear and explicit documentation). The secondary outcomes concerned the features of the policy: starting date, sanctions in case of non-compliance (and their nature), incentives, type of data shared and documents (IPD, and/or Code, and/or other documents such as protocol, clinical study report or statistical analysis plan), recommended data-sharing platforms (VIVLI, CSDR, YODA, SOAR, etc.), type of data request review panel (independent or not, or mixing independent members and funder members), data request methods (through data-sharing platform, by contacting trial investigators), specific funding for data-sharing, restriction of duration of data availability time frame for sharing data. We classified policies as being "encouraging policies" (policies that mention data-sharing without a strict requirement) or "mandatory policies" (policies that require the implementation of the recommendations and/or that mention sanctions in case of non-compliance). Lastly, the following features for each funder were extracted: country, World Bank income category (120), and whether it is a signatory of the Declaration on Research Assessment (DORA).

Survey of RCTs funded by funders with a data-sharing policy

Eligibility criteria and search strategy for RCTs funded by a funder with a data-sharing policy

For funders with a data-sharing policy, we examined the practical implementation of the policies. We initially planned to study published RCTs, however, as for most funders the date of implementation of the policy was not reported, it was impossible to judge whether or not any published RCTs was concerned by the data-sharing policy. The protocol was then amended to focus on data-sharing plans applying to registered RCTs. Any RCT registered after 1st January 2019 was then eligible without any distinction in terms of patients, intervention, comparator or outcome. Two-arm, multi-arm, factorial, cluster, and cross-over trials were included regardless their design (equivalence, non-inferiority or superiority).

RCTs were identified from the Clinicaltrial.gov website. We used the following filters to search for studies to include: the study starting date (after 1st January 2019), study type (interventional studies), funder type (industry filter for commercial sample, NIH and "all other" (a filter that identifies universities, charities and other funders) and filter for the non-commercial sample) . Among the RCTs found, we excluded studies where funders were not in our list of funders with data-sharing policies (a study was eligible if it was funded by at least one funder with a data-sharing policy identified in the first survey), and non-randomised studies. Then we selected two random samples of RCTs: 1/ one for non-commercial funders and 2/ one for commercial funders.

RCT data extraction

A data extraction sheet was developed. For each study included two authors (JG, MS) independently extracted the information entered in the "Individual Participant Data (IPD) Sharing Statement" field on the clinicaltrials.gov website. Disagreements were resolved by consensus and a third author (FN) was consulted in case of persistent disagreement.

Outcomes describing RCT data-sharing statements

The primary outcome for this second survey was the intention to share individual participant data in the data-sharing statements of eligible RCTs. The secondary outcomes were the features of the data-sharing statements: data-sharing plan in the registration, information about supporting material availability, information about the protocol and/or statistical analysis plan and/or clinical study report availability, data access methods, restrictions to data access, existence of a specific aim for data reuse, time frame for data availability, free accessibility of data.

Changes to the initial protocol

As stated above, we modified the methodology for assessing the compliance of RCTs with the sharing policies of their funders and focused on registered data-sharing plans in clinicaltrials.gov. This was done in accordance with the recommendations of ICMJE which states that "clinical trials that begin enrolling participants on or after 1 January 2019 must include a data-sharing plan in the trial registration".

We also made additional minor changes. When information was not publicly available on funder websites, we did not contact them to confirm absence or presence of a policy. Indeed, we previously carried out a similar study on French funders (121) in which the information on data-sharing policies was collected via a questionnaire with email reminders and/or calls in case of non-response. In this survey, we encountered difficulties in collecting the missing information because of failure to respond, but also difficulties in getting accurate information when funders did respond. We therefore decided to rely only on the policies published on the funders' websites. We also simplified funder eligibility, including funders with at least one RCT funded in the years 2016 to 2018 instead of one RCT funded per year over these 3 years, in order to cover a larger number of funders. Lastly, we added the list of the top 100 pharmaceutical companies in terms of drug sales in 2016 to complete the list of commercial funders. The detailed history of these changes is available on OSF (https://osf.io/ujbf2/).

RESULTS

Survey of funders' data-sharing policies

Funder selection and data extraction

Searches and extraction of eligible funders started on 15 February 2019 and ended with a consensus on 10 September 2019. One hundred and forty-nine non-commercial funders were identified from the Sherpa/Juliet website. Only 78 remained after applying our eligibility criteria and were included. Thirty-five commercial funders were identified from EFPIA, 27 from PhRMA, 37 from IFPMA, 67 from LEEM, along with the top 100 pharmaceutical companies in terms of drug sales, yielding 155 funders without duplicates. 103 of these met our inclusion criteria and 100 were randomly selected for inclusion. **Figure 4** details the selection process.

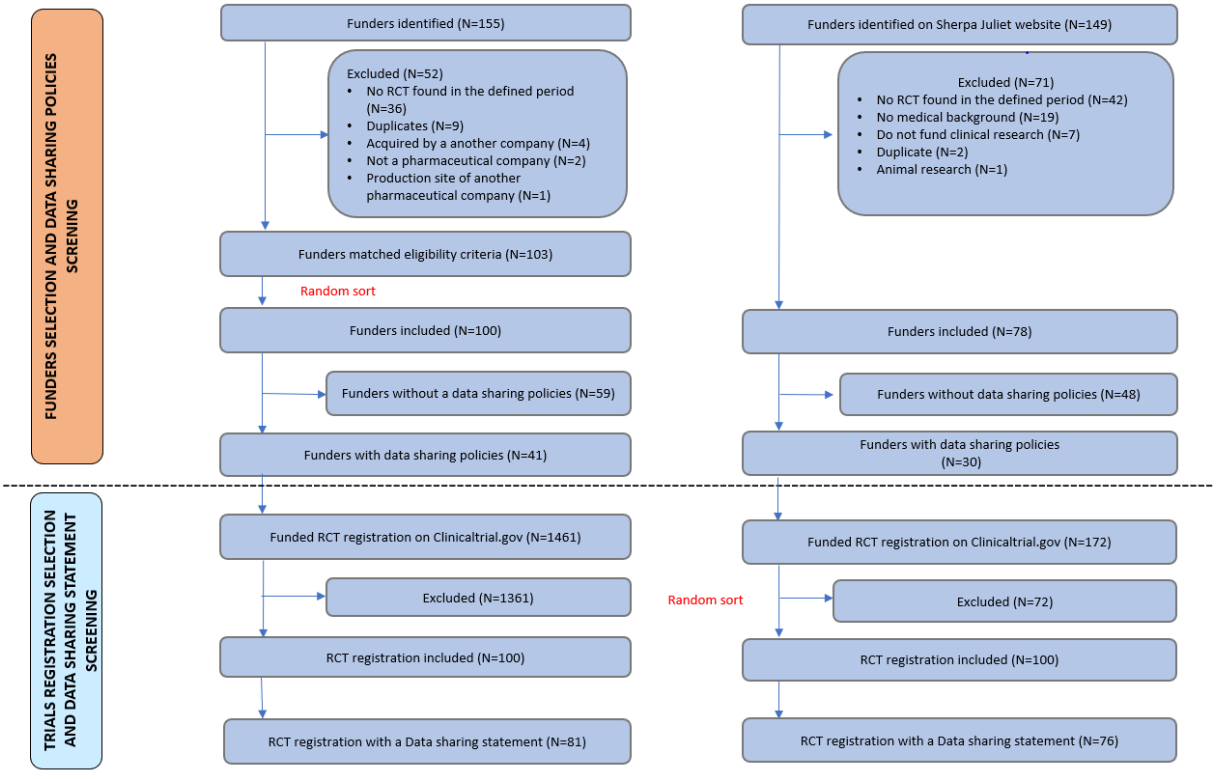

Figure 4: Funders and trials selection

Non-commercial funders

Of the seventy-eight non-commercial funders included, seventy-four (95%) were from high-income countries, two (2.5%) from upper middle-income countries and two (2.5%) were world organizations. Fifty-three funders (68%) were from Europe and central Asia, eighteen (23%) from North America, five (6%) were from east Asia and Pacific countries. The most widely represented countries were the UK (31 funders), the USA (9 funders) and Canada (9 funders). Twenty non-commercial funders (26 %) were DORA signatories.

Thirty (out of 78; 38%) non-commercial funders had a data-sharing policy. **Table 2** details the characteristics and policies of these funders. Eleven (37%) of the non-commercial funders with a data-sharing policy provided a starting date for their policies. Sixteen (53%) funders asked grant recipients to share data through data-sharing platforms or repositories, one specified the name of the platform (Clinical study data request) and another funder suggested several repositories like Dryad, Dataverse, Figshare and Zenedoo. In terms of sanctions, fifteen (50%) non-commercial funders mentioned that the review of the data-sharing plan was part of the funding decision and that non-compliance can lead to a suspension of the grant or refusal of a future grant application. Thirteen funders (43%) mentioned that they could provide funding to cover data-sharing costs. None of the funders mentioned incentives or rewards for sharing data in their policies.

Eighteen funders (60%) made data-sharing policies mandatory and twelve (40%) funders encouraged data-sharing. **Box 1 shows** some examples of the policies and **Figure 5.a** provides an overview of the words most frequently used in all the policies. Public funders' policies most often referred to the importance of the data management plan.

Extraction files used for this study and the relevant parts of policies, summarizing funders' positions on data-sharing are available on OSF (https://osf.io/ujbf2/).

	Non-commercial funders (N=30)	Commercial funders (N=41)
Mention of data sharing policy starting date	11 (37%)	17 (41%)
Data request methods		
Through data-sharing platform/data enclave/dedicated portal/repositories	16 (53%)	30 (73%)
By contacting trial investigators	0 (0%)	3(7%)
Mention of data-sharing platforms:		
VIVLI	0 (0%)	6(15%)
YODA	0 (0%)	1(2%)
CSDR	1(3%)	10(24%)
SOAR	0 (0%)	1(2%)
Type of shared data or documents mentioned?		
IPD	2(7%)	33(80%)
Code	0 (0%)	1(2%)
Other documents	1 (3%)	31 (76%)
Data request review panel		
Independent	0 (0%)	15(37%)
Internal review panel	1 (3%)	5 (12%)
Both	0 (0%)	6 (15%)
Specialist committee	0 (0%)	2 (5%)
Restriction of data availability time?	1 (3%)	2 (5%)
Specify time frames for data-sharing	9 (30%)	0(0%)
Existence of sanctions for non-compliance with policies?	15 (50%)	0(0%)
Reward for sharing data?	0 (0%)	0(0%)
Specific funding for data sharing?	13 (43%)	0 (0%)
DORA Signatory?	12 (40%)	0 (0%)

Table 2: Data-sharing features for funders with a data-sharing policy. *Data are presented as numbers (percentages)*

Commercial funders

Seventeen (out of 100, 17%) commercial funders included were generic pharmaceutical companies (generic pharmaceutical companies included were those that met our eligibility criteria, and therefore funded at least one clinical trial in the years 2016 to 2018). Ninety were from high-income countries, seven were from lower-middle income countries and three were from upper-middle income countries. The most widely represented countries were the USA (25 funders), Japan (16 funders) and France (13 funders). Forty-four were from Europe and central Asia, twenty-seven were from North America, twenty-two were from east Asia and Pacific countries and seven were from south Asia. None of the commercial funders were DORA signatories.

Forty-one (out of 100, 41%) commercial funders had a data-sharing policy that mentioned their commitment to make clinical trial data available on request (none of them was a generic pharmaceutical company). Thirty-one (out of 41, 76%) of funders with data-sharing policies are members of an organization with established data-sharing guidelines (PhRMA or EFPIA) and one (of 41, 2%) declares that it follows the principles without being a member.

Table 2 details the characteristics and policies of these 41 funders. Seventeen (41%) of them mentioned the starting date of their policies. Thirty (73%) mentioned that they shared their data through a data-sharing platform or a dedicated portal, and three (7%) after a direct contact from the requestor. The remaining funders did not provide details on requests. ClinicalStudyDataRequest was the most widely recommended data-sharing platform (24%). Thirty-three (80%) of the funders mentioned that they made IPD available on request. Thirty-one (76%) specified making other documents besides IPD available (e.g. clinical study reports, study level data, protocols). Concerning the examination of data requests, fifteen (37%) funders mentioned that data requests were evaluated by an independent review panel, five (12%) by an internal review panel, six (15%) mentioned both an internal and an independent panel and two (5%) mentioned a "specialist committee" without further information. Concerning the availability time for the data shared, only two of the funders specified a restriction on the duration of availability (data available for 24 months and data available for 12 months with a possibility for extension). None of the funders mentioned incentives or rewards for sharing-data, sanctions for non-compliance with the policy or funding for data-sharing procedures in their policies.

All commercial funder policies found supported data-sharing. Qualitatively, the distinction between "mandatory" and "encouraging" policies was not applicable because these policies did not apply to an external sponsor but to the commercial funder directly. The policies tended to contain statements supporting trial data-sharing allowing external researchers to request trial data. **Figure 5.b** and **Box 1** present a word cloud and some example of these types of policies.

The full data extracted for all funders is available on OSF (https://osf.io/ujbf2/).

Box 1: Example of supportive policy and mandatory policy

1.Supportive policies

*"**NIH believes that data sharing is essential** for expedited translation of research results into knowledge, products, and procedures to improve human health. NIH endorses the sharing of final research data to serve these and other important scientific goals and expects and **supports** the timely release and sharing of final research data from NIH-supported studies for use by other researchers." -National Institutes of Health (NIH)*

*"**We believe it is important to share clinical trial** data with the public and the scientific community. Sharing improves Research, Knowledge & Patient Care"- Servier*

*"The MRC **expects** valuable data arising from MRC-funded research **to be made available** to the scientific community with as few restrictions as possible so as to maximize the value of the data for research and for eventual patient and public benefit." - Medical Research Council*

2- Mandatory policies

*"All applicants seeking funding from Parkinson's UK will be **required** to submit a data sharing plan as part of their research grant application. If data sharing is not appropriate, applicants must include a clear explanation why." – Parkinson's UK*

*"It is essential that institutions and PIs share renewable reagents and data developed using Simons Foundation funds with other qualified investigators. PIs will be **required** to have a renewable reagents and data-sharing plan in place prior to receiving a grant"- Simons Foundation*

*"[…] All AHRQ-funded researchers **will be required** to include a data management plan for sharing final research data in digital format, or state why data sharing is not possible"- Agency for Healthcare Research and Quality*

5.a: Non-commercial funders ***5.b: Commercial funders***

Figure 5: Word cloud illustrating frequent words in funders' policies

Survey of RCTs funded by funders with a data-sharing policy

RCT selection and data extraction

Searches and extraction of eligible RCTs started on 27th September 2019 and ended with a consensus on 8th November 2019. One hundred and seventy-one study registrations on Clinicaltrial.gov were found for seventeen different non-commercial funders with data-sharing policies and six hundred and fifty-seven study registrations for thirty-six different commercial funders with data-sharing policies. **Figure 4** reports the selection process.

Non-commercial funders

The hundred trials randomly selected were funded by fifteen non-commercial funders. The most widely represented funders were NIH (61 trials) and Wellcome Trust (8 trials). A data-sharing statement was present for seventy-seven (77%, 95% IC [67 -84 %]) registered RCTs funded by non-commercial funders. Among the hundred registrations, 12% [7%-20%] had a "Yes" statement to IPD sharing and 12 % [7%-20%] an "Undecided" statement. 12% [7% - 20%] mentioned information about the availability of supporting material such as protocols (11% [6% – 19%]), statistical analysis plans (9% [4% – 17%]) and clinical study reports (6% [2 %– 13%]). The time period for data availability was specified in 11% [6 %– 19%] of the registrations. Six registrations [2% – 13%] specified that data would be freely accessible and 6% [2% – 13%] specified the methods to have access to data (email or website). **Table 3** details these data-sharing statements.

Commercial funders

The hundred trials randomly selected were funded by twenty-seven different funders. The most widely represented funders were Novartis (14 trials), Merck (10 trials) and GSK (10 trials). A data-sharing statement was present for eighty-one (81% [72% - 88%]) registered RCTs funded by commercial funders. Among the hundred registrations, 59 % [49% – 69%] has a "Yes" statement to IPD sharing, 9% [4% – 17%] an "Undecided" statement and 16% [10%-25%] a "No" statement (with 2 of them justifying that the reason for not sharing were respectively "the trial meets one or more of the exceptions described" and "individual participants could be re-identified"). 37% [28% – 47%] of RCT registrations mentioned information about the availability of supporting material. 12 % [7%– 20%] mentioned that data access would be limited to twelve months and 6 % [2% – 13%] that data would be made accessible for "viable scientific projects". Data requests were to be reviewed by an independent panel for 18 [11% – 27%] funders or by a mixed (internal and independent) panel for 2 [0.3% – 8%] funders. **Table 3** details these data-sharing statements.

	Non-commercial funded RCTs N=100	Non-commercial funded RCTs N=100
Data sharing plan in the registration?	77 [67% - 85%]	81 [72% - 88%]
Intention to share IPD		
Yes	12 [7% - 20%]	59 [49% – 69%]
Undecided	12 [7 % – 20%]	9 [4% – 17%]
No	54 [44% – 64%]	16 [10% – 25%]
Nothing specified	22 [15% – 32%]	16 [10% – 25%]
Information about supporting material availability?	12 [7% – 20%]	37 [28% – 47%]
Information about protocol availability?	11 [6% – 19%]	33 [25% – 44%]
Information about SAP availability?	9 [4%– 17%]	32 [23% – 42%]
Information about CSR availability?	6 [2% – 13%]	33 [24% – 43%]
Mention of timeframe of data availability?	11 [6%– 19%]	19 [12% – 28%]
Data will be freely accessible?	6 [2% – 13%]	26 [18% – 36%]
Mention of restriction of data access?	1 [0.5 %– 6%]	12 [7% – 20%]
Mention of a specific aim for data reuse?	3 [0.7 %– 9%]	6 [2% – 13%]
Mention of data access methods?	6 [2% – 13%]	47 [37%– 57%]

Table 3: Data-sharing statement details on trials registrations

Data are presented as percentages and their corresponding 95% confidence intervals

DISCUSSION

We found that 38% of non-commercial funders and 41% of commercial funders had a data-sharing policy in place, as mentioned on their websites. Most of the commercial funders are part of larger organizations (e.g. PhRMA, EFPIA) that have guidelines in place to implement data-sharing, so that commercial funders have more homogeneous attitudes toward data-sharing. In contrast, public funders showed broader heterogeneity in their recommendations. For non-commercial funders with a data-sharing policy, 60% made data-sharing mandatory and 40% encouraged data-sharing. The terms of the policies differ from one funder to another (non-commercial or commercial). Non-commercial funders' data-sharing policies contain recommendations for grant recipients to provide a data management plan and /or follow the FAIR principles, in most cases, as part of recommendations for a funding request. Commercial funder policies are more focused on request and means of access to individual patient data with supporting material (more often for a study in progress or completed) than on planning data-sharing upstream. Often policies lacked certain crucial information, as noted in previous audits (111) (112) (113). For instance, there was a lack of information on the existence of incentives and/or the type of data request review panel and/or on recommendation of specific platforms for non-commercial funders. Commercial funder policies often lacked information on sanctions and time frames for sharing data.

While we did not directly compare commercial and non-commercial funder enforcement of their policies, it seems that the data-sharing policies were more effectively implemented in data-sharing statements of trials funded by commercial funders: among RCTs registered on Clinicaltrial.gov, 77 % and 81 % respectively for non-commercial and commercial funders detailed a data-sharing plan, but 12% and 59% respectively expressed an explicit intention to share data. This result is in line with another important aspect of transparency, which is the observation that, despite being far from optimal, commercial funders perform better than non-commercial funders in ensuring availability of individual study results on registers such as clinicaltrials.gov (122) (123). In addition, the low percentages observed suggest difficulties in implementation of funders' data-sharing policies. These difficulties could result from a lack of understanding the policies (124) or from reluctance in the part of investigators (125). Planning upstream data-sharing and implementing it after a trial can be challenging.

As our audit points out, funders do not provide for incentives for data-sharing, and funding specially dedicated to data-sharing in not put in place by all of them. This lack of incentives and funding could hinder the implementation of the policies put in place. It is also possible that trialists registering their trial on clinicaltrials.gov do not attach importance to data-sharing plans at the time of registration. Importantly, the registration of a sharing plan (even if the plan was not to share data) was not 100% despite the fact that it has been made mandatory by the ICMJE for publishing an article in its member and affiliated journals. In addition, data-sharing plans were often unclear and some information was contradictory: in some registrations, it was indicated that there was "no plan to share IPD" while details were given about the procedure to access IPD. And indeed, a previous study (124) shared the same concerns and already noted that "several descriptions of IPD sharing plans reflected confusion or uncertainty about the term *IPD* and the meaning of the term *sharing"*.

Comparison with other studies

Estimates in our survey were different from the proportions of funders with data-sharing policies found in previous studies for commercial funders, but in the same range for non-commercial funders. While the methods and exhaustiveness of the previous surveys differed, making any direct comparison difficult, our results suggest that the proportion of funders with a data-sharing policy has not dramatically improved across the years. For commercial funders, the 2016 estimation (111) of 96 % was derived from a sample comprising the 25 biggest companies, and a 2018 survey (126) found that a data-sharing policy was available for 52% of a sample of 61 trials, funded by commercial funders (35 funders). For non-commercial funders, a 2017 survey (127) found 56% of non-commercial funders with a data-sharing policy in a sample of 18 funders.

Bergeris and al (124) examined responses on IPD sharing-related fields on Clinicaltrial.gov and found that 72% of the 35 621 trial records analyzed on August 31, 2017 had responded to the IPD sharing plan. Unlike our study, this study was carried out before the ICMJE requirement (128) and did not explore whether the registered studies included were indeed funded by funders with data-sharing policies. However, it was found that only 36.2% of the studies indicated an intention to share IPD or were undecided whether to share or not.

Strengths and limitations of the study

We tried to limit the selection bias by exploring a large, diversified, number of funders without focusing on only certain specific funders such as the top pharmaceutical industries. We relied on well-known lists of funders. However, to our knowledge, there is no existing exhaustive list of all possible funders worldwide and therefore a selection bias could persist. For instance, funders on the Sherpa list are mostly from the UK. We performed a similar survey on French funders (121) and found 9/31 (29%) funders with a data-sharing policy, corresponding to 19% (850.032.000 €) of the financial volume of the French funders surveyed. Only 2 of these French funders were also listed in the Sherpa list. Overall, these results suggest that our estimations are still subject to selection bias and could result in a possible overestimation of the number of funders with data-sharing policies. Furthermore, when we assessed registered trials, some funders were overly represented (such as the NIH among the public funders) reflecting the large number of trials they have funded in comparison with other funders.

We tried to limit the information bias by performing an independent extraction by two authors. However, some missing information (e.g. starting date of policy implementation, penalties for non-compliance…) was still likely, as the information about data-sharing policies was very poorly structured and heterogeneous across the different websites. A survey contacting the funders directly could have retrieved different information, with however the risk of non-response. For instance, it is possible that data-sharing policies are implemented but not mentioned or only partly described on the funders' websites. And this bias is perhaps less marked for commercial funders like the EFPIA, and PhRMA joint "Principles for Responsible

Clinical Trial Data Sharing" (129) stipulates that funders must have information pages dedicated to their data-sharing commitment. Lastly, funders' policies can change and it is likely that some funders that had no explicit policy when we performed our searches have now implemented one.

Perspectives

The suboptimal performances of funders in setting up and implementing data-sharing policies that we have highlighted in this study call for collective action. Misunderstanding (124), non-adherence (130), or lax application of recommendations are obstacles to consider.

Providing transparent information that reflects funders' commitments and positions toward data-sharing is one of the first important actions that funders can undertake in this direction. As a first step, the creation of an exhaustive list of funders and their policies would enable a continuous and systematic audit of their policies and research outputs.

However, existing policies are heterogenous, especially among non-commercial funders. As with commercial funders, groups of non-commercial funders could together define best practices with an agenda for implementation. It should also be noted that the recommendations for sharing data can be standardized to be applicable to clinical trials funded by commercial and non-commercial bodies (98). Involving researchers as well as trial participants in the design of best practices of this type is an initiative to be considered by funders, as it would make it possible to identify and address the most important leverages and concerns to consider when implementing effective data-sharing policies.

Moreover, providing evidence of the value of data-sharing will encourage the implementation of more effective policies. Any new policy should have an evaluation component, and we suggest that funders invest in studies on the global impact of their policies on the generation of new knowledge. In addition, any evidence of clinical data-sharing benefits will probably convince the community to adopt data-sharing policies. For instance, interventional trials comparing the impact of various data-sharing policies could explore outcomes such as the production of new knowledge, the enhancement of research reproducibility, and all the different promises of data-sharing. Again, convincing evidence that data-sharing produces the intended results could address the concerns expressed by some trialists (130) (131).

CONCLUSION

Funders have a key role to play in making data-sharing a standard in clinical research. Our survey shows that there is room for improvement with regard to their data-sharing policies. We call for a standardization of policies, with a strong evaluation component, to make sure that, when in place, these policies are effective.

SUPPORTING INFORMATIONS

The protocol and its amendments, the extracted data on the funders are available at https://osf.io/ujbf2/

2. Les financeurs français

Les politiques de partage de données des financeurs d'essais cliniques en France

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Jeanne Gaba a participé à la conception de l'étude (design, rédaction du protocole), à l'extraction des données, à l'analyse des données, à l'interprétation des résultats et à la rédaction de l'article.

RESUME

Objectifs

Les objectifs de cette enquête étaient d'évaluer le pourcentage de financeurs d'essais cliniques français ayant une politique de partage de données et de décrire les grandes lignes de leurs politiques en matière de partage de données et, de manière plus générale, de transparence de la recherche.

Méthodes

Les différents financeurs d'essais cliniques en France ont été identifiés à partir de 3 listes d'appels d'offres de projet de recherche clinique : la liste interne du Centre Hospitalier Universitaire (CHU) de Rennes, la liste du Groupement Interrégional de Recherche Clinique et d'Innovation (GIRCI EST), la liste du portail des appels à projets de la recherche en santé. Les financeurs étaient contactés, d'abord par email puis par téléphone (au moins deux relances email et/ou téléphoniques) afin de répondre à un sondage en ligne via Google Form. Le questionnaire visait à évaluer l'existence d'une politique de partage ou non, ainsi que la manière dont elle était mise en place.

Résultats

Sur 190 financeurs contactés, 94 n'ont pas répondu et 65 ont été exclus car ne finançaient pas d'essais cliniques. Sur les 31 financeurs inclus (parmi lesquels la DGOS, l'INCa, les GIRCIs), seuls 9 (29 %) avaient mis en place une politique de partage de données issus d'essais contrôlés randomisés (ECR) financés. Parmi ces neuf financeurs, un seul avait une politique rendant le partage obligatoire et huit une politique encourageant le partage. Cinq permettaient l'utilisation de lignes budgétaires dédiées au partage des données. Trois déclaraient octroyer des incitatifs au partage des données. Trois avaient des guidelines dédiées orientant vers un mode spécifique de partage de données concernant le modèle de partage (partage sur requête et/ou sur une plateforme spécialisée) et le type de données (données individuelles des patients et/ou protocole et amendements). Pour les trois, il y avait des restrictions vers un partage de données aux chercheurs uniquement. Le partage des données concernait 19% du volume financier total (850032000 euros) des 26 financeurs nous ayant déclaré cette information.

Conclusion

Malgré l'intérêt au plan international pour les pratiques de partage des données d'essais cliniques, les financeurs ayant une réelle politique de partage de données restent une exception en France.

Mots clés : Essai clinique, partage de donnée, transparence de la recherche.

INTRODUCTION

Les promesses d'un partage responsable des données issues des essais contrôlés randomisés (ECR) sont majeures avec la possibilité de réaliser des méta-analyses sur données individuelles, des analyses secondaires et des réanalyses. Des initiatives par des journaux scientifiques internationaux comme le British Medical Journal (BMJ) ou Public Library Of Science Medicine (101) ont été entreprises, afin de faire du partage des données des essais randomisés une réalité. En juin 2017, l'International Committee of Medical Journal Editors (ICMJE) a défini de nouvelles règles en matière de partage de données (132) et incite les chercheurs à spécifier un plan de partage des données dans leurs publications (c'est-à-dire à préciser les modalités fixées par la politique ICMJE pour un partage éventuel des données).

Au-delà de ceux qui publient la recherche, ceux qui la financent ont un rôle clef dans l'établissement de cette nouvelle norme. Certaines firmes pharmaceutiques ont développé des politiques de partage en mettant en ligne les données de leurs essais sur des plateformes comme la Clinical Study Data Request(133). D'importants bailleurs de fonds de la recherche clinique comme le Wellcome Trust, impose aux chercheurs qu'ils financent, de rendre disponible les données de recherche nécessaires à la réplication des analyses au moment de la publication(134).

Face à ces nouveaux standards internationaux, qu'en est-il des financeurs d'essais cliniques en France ? Plusieurs associations de patients, des syndicats de médecins et Médecins du monde ont lancé un appel à l'Institut National de la Santé et de la Recherche Médicale (INSERM) et au Centre National de la Recherche (CNRS) pour améliorer la transparence autour des ECR (135). Un plan national de science ouverte a été lancé le 4 juillet 2018 par le ministère de l'enseignement supérieur, de la recherche et de l'innovation (136) visant, entre autre, à rendre obligatoire la diffusion ouverte des données de recherche issues de programmes financés par appels à projets sur fonds publics. Dans ce contexte, les objectifs de cette enquête étaient d'évaluer le pourcentage de financeurs français ayant une politique de partage de données parmi ceux sélectionnés et de décrire les grandes lignes de leurs politiques en matière de partage de données et, de manière plus générale, de transparence de la recherche.

METHODES

Nous avons enregistré le protocole avant le début de cette enquête sur l'Open Science Framework (137).

Les différents financeurs français ont été sélectionnés à partir de 3 listes d'appels d'offres de projet de recherche clinique distincts :

- la liste interne du Centre Hospitalier Universitaire (CHU) de Rennes. La direction de la recherche clinique du CHU de Rennes tient une liste à jour des principaux appels à projets en recherche clinique et la diffuse auprès des enseignant-chercheurs du CHU ;

- la liste du Groupement Interrégional de Recherche Clinique et d'Innovation (GIRCI EST), qui est un portail commun aux 7 GIRCI répertoriant les informations sur les appels à projets de recherche en santé avec un moteur de recherche intégré permettant de faire le tri entre les subventions de recherche, les bourses postdoctorales, doctorales, de Master et les prix récompensant des travaux réalisés.

- la liste du portail des appels à projets de la recherche en santé, qui rassemble l'ensemble des appels à projets publics dans les domaines de la recherche translationnelle, clinique, et en santé publique. Il réunit neuf partenaires, lanceurs d'appel à projets de recherche dans ces domaines.

A partir de ces trois listes d'appels d'offres de projet de recherche clinique, nous avons inclus les financeurs proposant des subventions de recherches en France. Les financeurs proposant uniquement des bourses et/ou des prix et/ou du financement de matériel n'étaient donc pas inclus. Les financeurs n'ayant pas de site web, ni de numéro de téléphone joignable, ni de contact e-mail référencié n'étaient pas inclus.

Après un premier contact avec ces financeurs (ou en fonction des informations présentées sur leur site internet), étaient exclus ceux qui ne finançaient pas d'ECR. Au cours de l'étude, nous avons dû ajouter les critères d'exclusion suivant car d'évidence non adaptés : les universités, ambassades, et les intermédiaires entre chercheurs et financeurs. Enfin, lorsqu'un financeur était identifié via différents appels à projets, il n'était compté qu'une fois.

L'étude a été menée entre le 04 Avril 2019 (date de l'envoi du premier mail) et le 17 juin 2019 (date de la dernière réponse). Les financeurs étaient contactés, d'abord par email puis par téléphone (au moins deux relances par email et/ou téléphoniques) afin de répondre à un sondage en ligne via Google Form. Le questionnaire visait à évaluer les critères de jugement principal et secondaires. Le critère principal était l'existence d'une politique de partage. Lorsqu'une politique de partage était présente, les critères de jugement secondaires étaient : le type de politique de partage (politique rendant le partage obligatoire ou politique encourageant le partage), l'existence de lignes budgétaires dédiées au partage des données, l'existence d'un autre incitatif au partage des donnée (et, si oui, le type d'incitatif), l'existence de sanctions en cas de non-partage (et, si oui, quel type de sanctions), l'existence de guidelines pour un mode spécifique de partage de données (et, si oui, quel type de partage, c'est-à-dire partage sur requête ou sur différents types de plateforme), le type de données à partager (les données individuelles, le code statistique, et toute autre type de données), l'existence de restrictions vers un partage de données aux chercheurs uniquement. Le **Tableau 4** présente plus clairement ces différentes modalités.

Au-delà des critères portant sur le partage des données, d'autres aspects de leurs politiques étaient évalués pour tous les financeurs à savoir l'obligation d'un enregistrement préalable des recherches et l'existence d'incitatifs à la publication des résultats de l'étude (quel qu'étaient soit le résultat de l'étude).

Enfin, le sondage précisait les caractéristiques du financeur à savoir le nombre d'appels d'offres du financeur sur l'année 2018, le volume financier annuel (2018) de l'ensemble des appels d'offres de ce financeur.

Les réponses au questionnaire ont été rapportés et décrits sous forme d'effectifs, de pourcentages, de médiane (et intervalles interquartiles). Les analyses statistiques ont été réalisées à l'aide du logiciel R (138).

RESULTATS

La figure 6 représente les différentes étapes de sélection des financeurs d'ECR inclus dans notre enquête. Parmi les 276 financeurs identifiés, 86 ont été exclus. Sur les 190 contactés, le taux de réponse était de 51%. 65 des financeurs contactés et ayant répondu ont été finalement exclus car ils ne finançaient pas d'ECR. Nous avons alors inclus et analysé les réponses de 31 des financeurs contactés. La liste des financeurs analysés est présentée dans l'**annexe 1**.

Le tableau 5 présente les caractéristiques descriptives des financeurs inclus selon l'implémentation d'une politique de partage ou non. Le volume financier sur l'année 2018, le nombre d'appels d'offres sur l'année 2018, réglementation sur l'enregistrement des ECR financés et la publication des résultats quel que soit le résultat sont les questions communes à tous les financeurs inclus. Sur les 31 financeurs inclus, les informations concernant le nombre d'appels d'offres et/ou le volume financier ne nous a pas été communiqués pour 5 d'entre eux.

Parmi les 31 financeurs d'essais cliniques français inclus, seuls 9 (29%) déclarent avoir une politique de partage de données avec une obligation d'enregistrement préalable des ECR pour six d'entre eux. 13 (42%) financeurs déclarent rendre obligatoire la publication des résultats (qu'ils soient positifs ou négatifs), dont 6 ayant une politique de partage de données. 6 (27%) des financeurs n'ayant pas déclaré de politique de partage de données rendent obligatoire l'enregistrement préalable des ECR.

Le nombre d'appels d'offres médian en 2018 des financeurs inclus est de 2. Le volume financier médian des appels d'offres en 2018 est de 420000 € pour les financeurs ayant déclaré une politique de partage et de 1400000 € pour ceux n'en ont pas déclaré. Les dix principaux financeurs en termes de volume financier parmi ceux inclus sont listés dans le **tableau 6.** La **figure 7** présente la part en termes de nombre d'appels d'offres et de volume financier sur l'année 2018 des financeurs des essais cliniques qui déclarent avoir une politique de partage de données. Le partage des données concernait 19% du volume financier total (850032000 euros) des 26 financeurs nous ayant déclaré cette information.

Critère de jugement	Modalités	Explications
Type de politique de partage	**Obligatoire**	Le partage des données est rendu obligatoire par le financeur. Par exemple, la fondation Bill and Melinda Gates impose que « les données ayant servi à produire tous les résultats publiés seront accessibles et ouvertes immédiatement » (https://www.gatesfoundation.org/how-we-work/general-information/open-access-policy)
	Incitative (encourageant le partage)	Le financeur encourage les chercheurs à partager sans que cela ne soit une condition obligatoire pour être financé. Il peut pour cela mettre en places différents incitatifs.
Existence d'incitatifs	**Lignes budgétaires**	Le financeur met à disposition des chercheurs des lignes financières dédiées à la préparation et au stockage des données. Le partage des données impose en effet une préparation pour rendre les données réutilisables et garantir la sécurité des patients.
	Autre incitatif	Pour cette catégorie, nous acceptions tout type d'incitatif. Le financeur peut par exemple conditionner le financement de projets ultérieurs au partage des données lors de financements antérieurs.
Existence de sanctions en cas de non-partage		Pour cette catégorie, nous acceptions tout type de sanction. Par exemple, le financeur pourrait décider de ne pas verser la dernière part de budget en cas de non partage.
Existence de guidelines pour un mode spécifique de partage de données	**Partage sur requête**	Ce mode de partage se fait par contact (par exemple email) entre les chercheurs souhaitant les données et les chercheurs disposant des données.
	Partage sur une plateforme dédiée	Les données sont déposées sur de larges plateformes de partage de données comme Vivli, the Yale Open Data Access (YODA) Project ou encore Clinical Study Data Request.
Type de données à partager	**Données individuelles**	Les données individuelles des patients issus des essais cliniques sont disponibles au partage.
	Code statistique et autre type de données	Le partage des données va au-delà des données individuelles : le code statistique, les rapports d'études, le plan d'analyse statistique, le protocole sont aussi concernés par la politique de partage.
Restrictions vers un partage de données aux chercheurs uniquement.	**Existence de restrictions**	Le partage des données ne se fait qu'entre chercheurs.
	Aucune restriction	Le partage des données peut se faire avec des chercheurs, mais aussi avec tout autre acteur, comme par exemple des associations de patients, des journalistes, des citoyens, des industriels…

Tableau 4: Les différents éléments des politiques de partages pris en compte

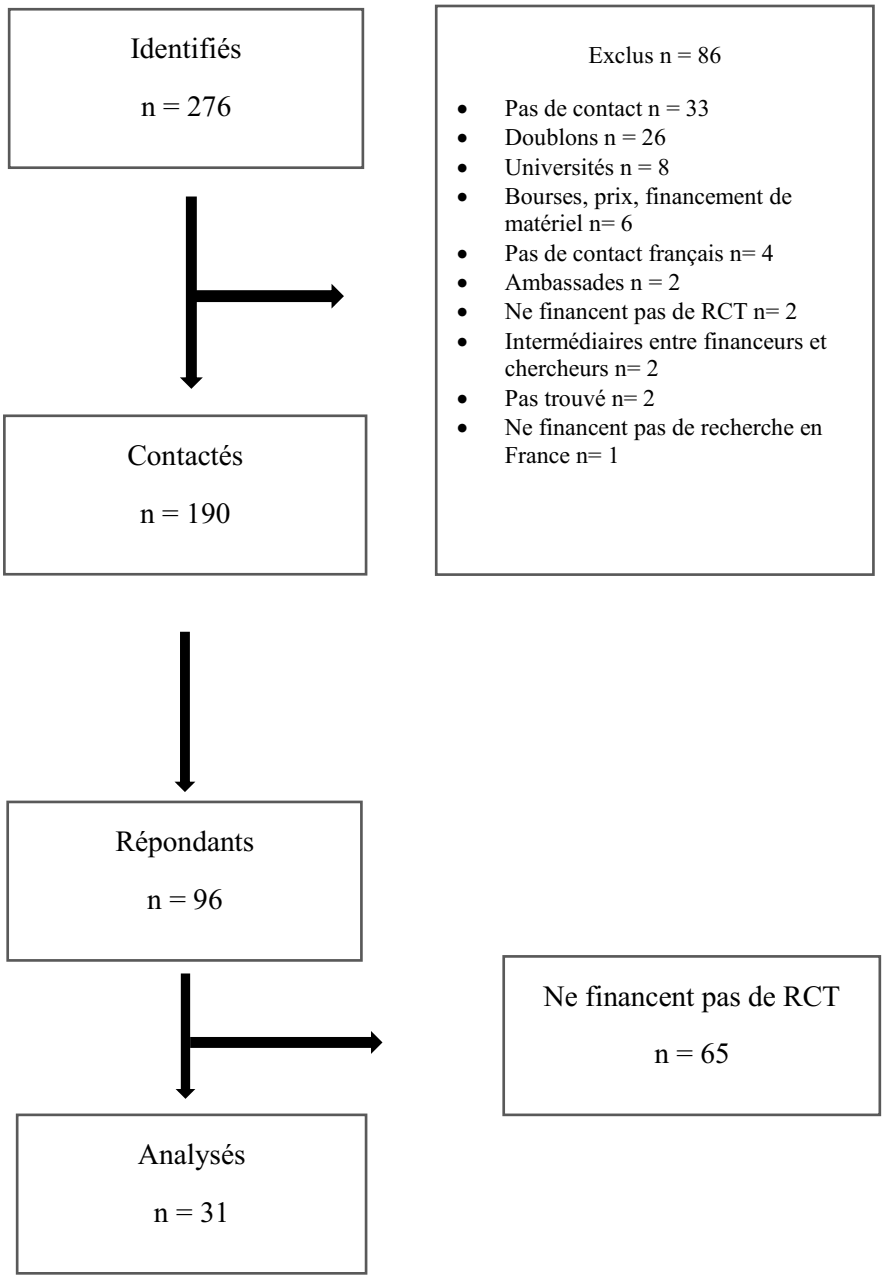

Figure 6: Sélection des financeurs d'essais cliniques en France

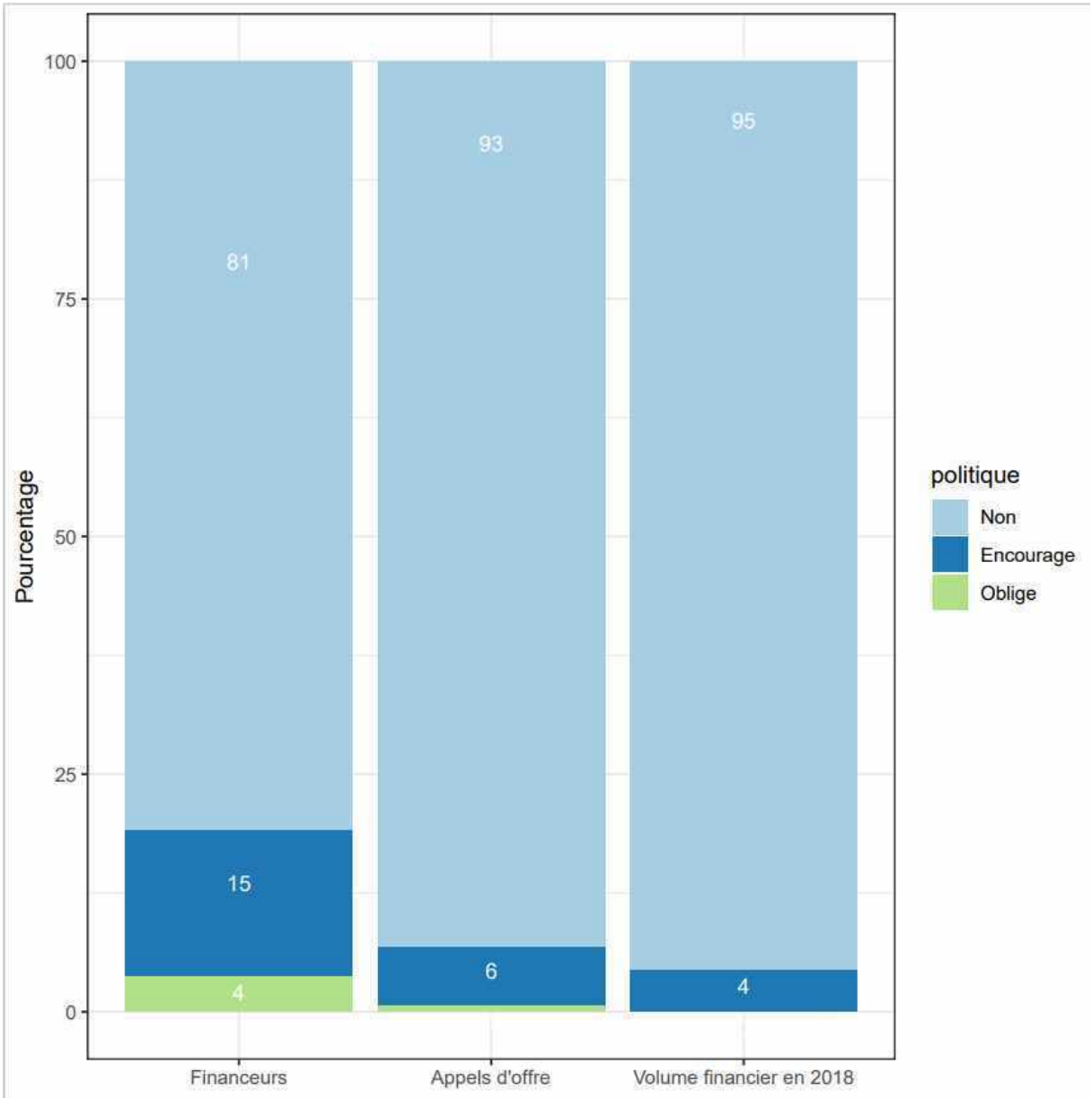

Figure 7: Part des politiques de partage de données en termes de volume financier et de nombre d'appels d'offres

Le **tableau 7** présente les caractéristiques des politiques de partage de données recueillies via le questionnaire. Trois financeurs ont déclaré avoir des guidelines orientant vers un mode spécifique de partage de données (le partage sur requête et/ou le partage via une plateforme spécialisée) avec une restriction du partage aux chercheurs uniquement. Les types de données disponibles au partage sont : les données individuelles des patients, le protocole et ses amendements. 5 financeurs déclarent dédier des lignes budgétaires au partage de données dont 3 ont mis en place des incitatifs au partage. La ligue contre le cancer est le seul financeur à avoir fourni un détail des incitatifs : une aide aux investigateurs pour l'organisation du recueil d'analyse de données au plus haut niveau scientifique à travers des financements de plateformes de recherche clinique. Pour un autre financeur, l'incitatif déclaré n'était pas clairement exprimé et nous n'avons pas pu avoir confirmation malgré plusieurs relances.

	Financeurs inclus N=31(100)	**Financeurs ayant une politique de partage de données N= 9 (29)**	**Financeurs n'ayant pas de politique de partage de données N=22 (71)**
Enregistrement obligatoire des ECR financés	12 (39)	6 (67)	6 (27)
Publication obligatoire des résultats des ECR financés	13 (42)	6 (67)	7 (32)
Nombre d'appels d'offres médian en 2018	2 (1-5)	2 (1.5 – 4)	2 (1 - 5)
Volume financier médian des AO en 2018	1100000 (362500-6590000))	420000 (253000-1000000)	1400000 (400000-7620000)

Tableau 5: Caractéristiques des financeurs d'ECR français ayant une politique de partage de données par rapport à ceux qui n'en ont pas.

Les résultats sont sous forme de nombre (pourcentage) pour les variables qualitatives et de médiane (interquartile range) pour les variables quantitatives.

	Volume financier (euros)	Nombre d'appels à projets	Politique de partage de données
Agence Nationale de la Recherche	600 000 000	50	Non
Direction Générale de l'Offre de Soins	130 000 000	8	Non
Ligue contre le cancer	36 500 000	9	Encourage le partage de données
Vaincre la mucoviscidose	24 000 000	1	Non
Institut National Contre le Cancer	22 000 000	4	Non
Hospices Civils de Lyon	12 000 000	150	Non
Fondation APICIL	7 620 000	4	Non
GIRCI EST	3 500 000	3	Non
GIRCI GRAND OUEST	2 800 000	1	Non
Fondation ARSEP	2 280 000	1	Non

Tableau 6: Volume financier et nombre d'appels d'offres des dix plus gros financeurs, déclarés lors de notre enquête

Tableau 7: Caractéristiques des politiques de partage de données

Les résultats sont sous forme de nombre (pourcentage)

	Financeurs ayant une politique de partage de données N= 9 (29)
Type de partage de données	
Encourage le partage	8 (89)
Oblige le partage[1]	1(11)
Lignes budgétaires allouées au partage	
Oui[2]	5(56)
Non	4(44)
Récompenses en cas de partage	
Oui[3]	3 (33)
Non	6 (67)
Sanctions en cas de non-partage de données :	
Oui	
Non	9 (100)
Mise en place de guidelines dédiées au PD :	
Oui[4]	6 (67)
Non	3(33)
Mode de partage recommandé :	3(33)
Dont sur requête[5]	1
Dont sur des plateformes[6]	1
Dont les deux[7]	1
Types de données partagées :	
DIP[8]	1(33)
DIP +Protocoles et amendements[9]	2(67)
Partage de données uniquement aux chercheurs[4]	3 (33)

Association pour la Recherche sur la Sclérose Latérale Amyothropique[2,4,5,9], Société Francophone d'Arthroscopie[2], Association Hubert Gouin[2,3], La ligue contre le cancer[2,3], Association Française d'urologie[2,3,4,7,9], GIRCI Nord-Ouest[1], Institut National de la Santé Et de la Recherche Médicale, Société Française de Cardiologie, Institut de Recherche sur la Moelle Epinière[4,6,8]

DISCUSSION

Sur les 31 financeurs analysés, 29 % des financeurs français avaient une politique de partage de données issues d'ECR. Plus précisément, parmi les 10 plus gros financeurs que nous avons pu identifier en termes de volume financier, un seul a déclaré faire du partage des données une possibilité encouragée.

Dans un échantillon international de 18 financeurs majeurs, 2 (11 %) avaient une politique imposant le partage et 9 (50 %) une politique incitant au partage (113). Toute comparaison reste difficile, mais en tout état de cause, les politiques de partage de données obligatoire restent l'exception aussi bien à l'international qu'en France. Par contre, en ce qui concerne, les politiques encourageant au partage, celles-ci sont presque inexistantes en France alors qu'elles sont clairement plus développées à l'étranger.

Il est difficile d'obtenir une liste complète des financeurs de la recherche clinique en France. Pour avoir une liste plus exhaustive, les financeurs analysés dans notre étude ont été sélectionnés en croisant trois listes différentes d'appels d'offres majeures. Mais ces listes ne comprenaient pas que des financeurs d'essais randomisés contrôlés : il y avait des régions, des ambassades et des financeurs que bon nombre de chercheurs en recherche clinique n'ont pas l'habitude de contacter. La mise en place d'un registre listant les différents bailleurs de fonds de la recherche clinique en France pourrait être un plus pour une meilleure diffusion de l'information. Ce serait un moyen efficace pour un chercheur d'avoir des informations sur les possibles bailleurs de fonds pour sa recherche et les différents politiques de ces derniers en matière de partage de données et tout autre mesure ayant pour but d'améliorer l'intégrité et la qualité de la recherche. Un exemple de ce type de registre est « Sherpa-Juliet » qui récence les conditions des bailleurs de fonds pour une publication en « open access » (139). Il existe aussi des interfaces universitaires pour informer les chercheurs sur les recommandations des bailleurs de fonds ayant une politique de partage de données et Open Access (140).

Nous avons rencontré des difficultés à contacter les financeurs : pour certains nous n'avions aucunes coordonnées ni téléphoniques, ni mail et pour d'autres, nous n'avons pas reçu de réponses malgré nos relances (les personnes répondants au téléphone ou par mail ne sachant parfois pas nous orienter). Cependant, nous avons pu collecter des informations sur les principaux financeurs d'essais cliniques à savoir la DGOS (Direction Générale de l'Offre de Soins), l'INCa (Institut National du Cancer) et les différentes GIRCI (Groupement Interrégional pour la Recherche Clinique et l'Innovation). Nous avons aussi pris en compte la réponse de l'ANR qui apparaît comme l'agence ayant le plus gros volume financier. Néanmoins, la part de la recherche clinique dans les financements de l'ANR est faible et assurément moins importante que celle de la DGOS qui s'occupe du lancement des programmes de recherche financés par le Ministère des solidarités et de la santé. Le programme hospitalier de recherche clinique (PHRC) est l'un de ces programmes et il constitue l'un des plus importants financements de la recherche clinique en France. Le PHRC se décline en trois appels à projets : le Programme Hospitalier de Recherche Clinique national (PHRC-N), le Programme Hospitalier de Recherche Clinique en cancérologie (PHRC-K) dont la gestion est assurée par l'INCa, le Programme Hospitalier de

Recherche Clinique inter-régional (PHRC-I) dont la gestion est assurée par chaque GIRCI. Le suivi des projets retenus s'appuie sur un découpage en phases de leur déroulement et conditionne leur financement, adapté à l'avancement de la recherche. En plus du PHRC, les GIRCI possèdent une enveloppe interne qui leur permet de financer des projets de recherche qui peuvent être de la recherche clinique.

Notre questionnaire a été construit pour récolter les informations sur les politiques de partage mais pouvait passer à côté de subtilités, que seule une approche plus qualitative pourrait mieux appréhender. Une approche plus qualitative aurait permis une vérification supplémentaire des réponses recueillies et aussi prendre en compte les décisions à venir des financeurs sur les notions de transparence et de réutilisation des données issues des essais cliniques. Par exemple s'il est clair que la DGOS n'a pas de politique de partage des données, elle n'est pas fermée à ces questions. Nos échanges avec ce financeur soulignent que des lignes de budget pour un partage de données pourraient être discutées au cas par cas. Indirectement, la politique de suivi des projets financés de la DGOS a pour but de permettre une meilleure visibilité et d'encourager le partage des résultats.

Les financeurs analysés dans notre étude sont pour la plupart des institutions gouvernementales, des associations et/ou des fondations dont les principales ressources financières proviennent de dons. Bien que notre étude montre une méconnaissance du partage de données dans le secteur public, il n'en est pas forcément le cas au niveau de certains industriels français (secteur pas pris en compte dans notre étude). Bien que politique de partage n'implique pas toujours un partage effectif, la Fédération Européenne des Industries et Associations Pharmaceutiques (EFPIA) a une politique de partage de données et les membres français suivent cette politique en rendant disponible les données issues des ECR et d'autres documents dans un but de transparence et de reproductibilité. De plus, l'agence Européenne du médicament a prévu de rendre obligatoire le partage avec sa politique 0070 de 2014 (141). Cette prise de conscience de l'importance du partage de données doit être repensé au-delà de la réglementation des médicaments et être un des critères d'évaluation de la recherche clinique. Au-delà des financeurs, les initiatives de partage des données doivent impliquer les promoteurs et les responsables scientifiques des essais. Ceux-ci sont généralement considérés, à tort ou à raison, comme « propriétaires » de ces données et ont nécessairement un rôle important. Si les sondages à l'international, comme par exemple celui de Rathi *et al*. (142) révèlent généralement des intentions de partage élevées chez les investigateurs, il serait intéressant de réaliser un sondage, au plan français se focalisant sur les investigateurs et les différentes directions de la recherche clinique. Il serait intéressant d'y ajouter une partie qualitative explorant leurs perceptions en termes de valorisation de la recherche et leurs représentations sur le partage dans le contexte international actuel.

Mais, aucune initiative isolée ne saurait suffire. Par exemple, deux journaux d'envergure, le BMJ et PLOS Medicine ont imposé le partage des données pour les études randomisées qu'ils publiaient. La disponibilité des données n'était pas optimale mais le taux de partage des données de l'ordre de 50 % était plus élevé qu'ailleurs dans la littérature biomédicale (101). Les problèmes de contact avec les auteurs correspondants, le manque de ressources dans la

préparation des ensembles de données et l'importante hétérogénéité des pratiques de partage des données sont autant d'obstacles à surmonter.

Le partage des données, est présenté par l'ICMJE comme un impératif d'ordre éthique (143). En d'autres termes puisque les participants aux essais acceptent de prendre des risques, on leur doit en retour une utilisation optimale des données générées par la recherche. D'ailleurs, dans une étude américaine, les patients étaient dans une très large majorité favorable au partage de leurs données (112). Le partage responsable des données maximiserait en effet les bénéfices que l'on peut attendre des essais en permettant des méta-analyses sur données individuelles, en permettant d'explorer des questions nouvelles sans avoir besoin de faire courir de nouveaux risques dans une nouvelle étude lorsqu'un jeu de données existe déjà et en permettant des ré-analyses pour certaines études parfois controversées. Les financeurs sont assurément un levier supplémentaire pour faire du partage des données des essais thérapeutiques une réalité. Le partage de données n'est pas sans contraintes et les financeurs peuvent allouer les ressources manquantes aux équipes pour mettre en forme, anonymiser et transférer les données dans les conditions les plus sûres possibles. Au-delà d'imposer le partage, ils peuvent imposer qu'une information adaptée et claire sur ce partage soit donnée aux scientifiques et aux patients. Ils ont une responsabilité certaine à assurer une utilisation optimale des ressources qu'ils allouent et à éviter autant que possible le gaspillage des efforts de recherche. Bien entendu, les questions sont nombreuses quant au type et aux modalités des politiques à adopter. Au Royaume Uni, le Medical Research Council Hubs for Trials Methodology Research a proposé un modèle de partage des données individuelles sur requête raisonnable des études ayant reçu un financement public (144). Au-delà, en faisant du partage des données, de la publication de tous les résultats, et d'autres pratiques de sciences ouvertes des critères servant à l'allocation des ressources, les financeurs pourraient contribuer à mieux aligner le système actuel d'incitatifs et de récompenses sur les besoins de la société et à valoriser la qualité des travaux scientifiques (145).

Nous pensons qu'il est temps de réunir les principaux financeurs et acteurs de la recherche clinique française pour définir d'une politique efficiente de partage, concrète, réfléchie et de mettre en place une évaluation des bénéfices apportées par ces politiques. Une telle politique de partage devra bien entendu prendre en compte la réglementation française relative à la protection des données et le Règlement Général sur la Protection des Données (146). Elle devra aussi prendre en compte le positionnement des patients inclus dans les études pour lequels les attitudes vis-à-vis du partage sont positives (147). Qui plus est toute politique devrait être associée une composante d'évaluation afin de voir si le partage mis en place assure les bénéfices attendus. L'enjeu est de maximiser la valeur du bien public inestimable que représentent les données de la recherche clinique.

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CHAPITRE 3 : L'établissement des politiques de partage de données garantit-il le partage réel des données ?

RESUME

Le partage et la réutilisation efficaces des données des essais cliniques sont essentiels pour faire progresser les connaissances médicales et développer des traitements améliorés. En prenant le cas de l'ICMJE, nous montrons que les plans de partage de données ne garantissent pas le partage réel des données. Nous pensons que la politique de partage de données de l'ICMJE est actuellement inadéquate et proposons l'adoption d'une politique plus forte sur le partage de données, qui soit rigoureusement appliquée dans toute les revues membres et affiliées. Cette politique doit être dotée de moyens d'évaluation pour mesurer la valeur des exigences de partage de données. En plus des changements à la politique de l'ICMJE, nous proposons des actions conjointes avec les autres parties prenantes de la recherche telles que les chercheurs et les financeurs pour faire du partage de données la norme en recherche clinique.

Medical journal requirements for clinical trial data sharing: Ripe for improvement

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Summary points :

- Efficient sharing and re-use of data from clinical trials is critical in advancing medical knowledge and developing improved treatments.

- We believe that the International Committee of Medical Journal Editors (ICMJE) clinical trial data-sharing policy is currently inadequate.

- Although data-sharing plans help increase transparency, they do not ensure that data are shared, and they are often inadequately implemented.

- We believe that the ICMJE should adapt a stronger policy on data sharing that is enforced rigorously in all ICMJE member and affiliated journals.

- The policy should include a strong evaluation component to ensure that all clinical trial data are shared, their value maximized and data producers incentivized.

In some STEM (Science, Technology, Engineering, and Mathematics) fields, data-sharing is the norm (e.g. physics or space science). However, this is currently not the case in biomedicine, except for certain exceptions in areas such as genomics. For therapeutic research, data-sharing is expected to maximize the value of research for clinical practice by means of greater transparency and opportunities for external researchers to re-analyze, synthesize, replicate and build upon previous evidence. Examples include re-analyses, secondary analyses, Individual Patient Data (IPD) meta-analyses, and methodological evaluations. Maximising the efficient use of clinical research data is important in the development of new therapeutic options, including treatments for COVID-19.

However, despite the prominent role of clinical trial data in evidence-based medicine, data-sharing in clinical trials was almost non-existent even years after the United States National Institutes of Health (NIH) recognized its value in their 2003 Data-Sharing Policy [1]. In the past 10 years, several initiatives leading to research infrastructures (repositories) have been launched to promote data sharing, including data repositories such as the Clinical Study Data Request [CSDR] and the Yale University Open Data Access [YODA]. Overall, there has been a lack of effective policies to ensure that study data are maximally available and reusable: certain journals require data-sharing but their guidelines have been inconsistent and unclear [2]. A minority of publishers or journals, such as PLOS and the *British Medical Journal* (BMJ), have stronger data-sharing requirements [3].

Several influential groups have developed data-sharing guidance and policies. In 2016, the International Committee of Medical Journal Editors (ICMJE, which currently has 14 journal and organizational members), published a proposal [4] stating that there is an ethical obligation towards trial participants who have volunteered and put themselves at risk to help generate information about the safety and efficacy of interventions, to responsibly share clinical trial data. The ICMJE suggested that de-identified IPD should be made publicly available no later than 6 months after publication of the main trial results. However, this proposal triggered debate, and many investigators have expressed skepticism towards this proposal [5]. The concerns raised include the feasibility of the proposed requirements for data sharing, the resources needed, the real or perceived risks for trial participants, and the need to protect the interests of patients and researchers. Some of those concerns were found to be unwarranted. For example, survey evidence suggests that patients are willing to have their data shared in a responsible and secure manner [6]. Nevertheless, the ICMJE moderated their initial proposal. Their final requirements did not make data-sharing mandatory, but required a data-sharing plan to be included in each paper from the July 1st 2018 and pre-specified in study registration for clinical trials beginning enrollment of participants after January 1st 2019, as a condition for publication [7]. However, outputs of the Reproducibility in Therapeutic Research program suggest that this policy is unlikely to be met with current practices [8-10]. Although a data-sharing plan is not enough to ensure that data are shared [3], even this basic, first step is insufficiently implemented.

Performance of the ICMJE data sharing policy

Journals considered by the ICMJE as affiliated journals (i.e. journals stating that they follow the ICMJE recommendations) are not mandated by the ICMJE to respect the ICMJE policy, and there is no ICMJE data-sharing dashboard to monitor data-sharing activities. The ICMJE clearly states that ICMJE "cannot verify the completeness or accuracy" of the list of affiliated journals (see the ICMJE website: http://www.icmje.org/journals-following-the-icmje-recommendations/). Indeed, there is suboptimal implementation of ICMJE data-sharing requirements among the ICMJE-member journals themselves. For instance, in 2019 (at this time there were 14 member journals), 8/14 had an explicit data-sharing policy (including 3 more stringent, and 1 less stringent than the ICMJE requirements); 5/14 had a statement that they followed ICMJE requirements without further details; and 1/14 had no policy on their website [8]. Additionally, the ICMJE website outlines that many affiliated journals may not follow their recommendations. In addition, despite some uncertainty regarding the definition of predatory journals, evidence suggests that around 30 % of affiliated journals are potentially predatory journals [11], with editorial practices that "deviate from best editorial and publication practices" [12]. It is unlikely that such journals have any effective data sharing policy in place.

In an analysis of 489 randomly selected ICMJE-affiliated journals that published a randomised controlled trial (RCT) in 2018, with an accessible online website and not considered as potentially predatory journals, 30% (95% confidence interval [CI]: 26% - 34%) had an explicit data-sharing policy on their website [8]. Of these, 7% were more stringent, 59% were less demanding, and 34% were compliant with the ICMJE policy. Furthermore, 56% of the sample (95% CI: 52% - 61%) only referred to ICMJE requirements, and 14% (95% CI: 11% - 17%) had no data-sharing policy and their instructions did not allude to the ICMJE recommendations.

In a random sample of 100 articles on RCTs published in 2019 in the 14 ICMJE-member journals, there were data-sharing statements in 98% (95% CI: 92% - 99%). However, data-sharing statements can simply state that "no data are available" [8]. An intention to share IPD was expressed in 77% (95% CI: 67% - 85%) of articles. However, in a random sample of 100 articles published in 2019 on RCTs published in ICMJE-affiliated journals with a data-sharing policy, there were data-sharing statements in only 25 % (95% CI: 17% - 35%) and intention to share IPD was expressed in 22% (95% CI: 15% - 32%).

According to an evaluation of 487 RCTs with a data-sharing statement published in *JAMA, The Lancet,* and *NEJM* between July 1st 2018 and April 4th 2020, only two (0.5%) of the 334 RCTs declaring they shared data had de-identified IPD available on the journal website that could be downloaded and reused. Another 89 (27%) articles proposed to store data in repositories, but data were stored for only 17 studies, mostly because of restrictions due to embargo periods pending product approval. The remainder were described as being accessible via request to a committee, authors or company and unspecified for 15 (5%) [13].

While data-sharing statements are an important first step, a promise to share data does not guarantee that data will be made available when requested. A previous analysis of RCT articles published in *BMJ* and *PLOS Medicine*, two prominent medical journals with a policy requiring

RCT data-sharing (since January 2013 for RCTs on drugs and devices and July 2015 for all therapeutics for *BMJ*, and after March 2014 for all types of interventions for *PLOS Medicine*), found that for only 46% (95% CI: 30% - 62%) of the eligible studies had the original investigators shared their data with sufficient information to enable re-analysis [3]. For trials submitted and published subsequent to the adoption of data-sharing policies by these journals, 24% of de-identified IPD were retrievable for downloading and use, 65% were declared available upon request, 3% were embargoed and 8% were declared not available.

The ICMJE also requires data-sharing plans for registered trials: "clinical trials that begin enrolling participants on or after 1 January 2019 must include a data-sharing plan in the trial registration" [7]. Indeed, there are certain important issues (such as those related to informed consent) that should ideally be pre-specified and fixed before the trial is started to make data-sharing possible in practice. However, here, the implementation of the policy is worse, even for trials supported by funders with data-sharing policies promoting IPD sharing. A 2019 survey of RCTs registered on ClinicalTrials.gov by funders with a data-sharing policy found that data-sharing plans were present for 77% (95% CI: 67% - 84%) and 81% (95% CI: 72% - 88%) of RCTs funded by non-commercial and commercial funders respectively [9]. An expressed intention to share data was found in 12% (95% CI: 7% - 20%) and 59% (95% CI: 49% - 69%) of RCTs funded by non-commercial and commercial funders respectively.

Beyond data sharing to data re-use

Although data availability is a prerequisite for effective re-use of the data, it is actual re-use of data that leads to the expected benefits of clinical trial data-sharing. However, actual re-use of data is difficult to gauge. The *Annals of Internal Medicine* has encouraged, although not required, data-sharing since 2007, but over the subsequent decade articles expressing an intention to share data were not associated with published re-use of data (i.e. re-analysis, secondary analysis, or IPD meta-analysis) [10]. Arguably, authors who commit to data-sharing may in fact be reluctant to share their data. They may be insufficiently incentivized for data-sharing, as the current evaluation of scientists relies on traditional criteria (e.g., productivity in terms of authored publications) as opposed to progressive criteria (e.g. data-sharing) [14]. Furthermore, authors are often difficult to contact and may lack the time, knowledge, technical infrastructure, or financial resources to prepare and share the datasets [3]. In addition, authors may not be aware of the resources available to facilitate data-sharing and may face legal difficulties in sharing their data, as the definition of "anonymization" is not universal (e.g. in the European context), can be ambiguous, and carries a risk of loss of information [15].

It is also possible that data are not requested; indeed, usage metrics from repositories such as YODA and CSDR suggest that a large majority of data is not requested or that re-uses may remain unpublished. Practical issues could contribute to this problem, as the process of data-sharing on these platforms is still cumbersome and data shared without codes or proper dictionaries may be impossible to re-analyze and re-use. An alternative possibility is that many trials where data become available are small, or poorly designed studies presenting little interest

for re-use of their data, while large, pivotal trials often fail to offer data-sharing. For instance, the Data Ark initiative was unable to retrieve data from the majority of the most widely-cited studies published between 2006 and 2016 in the fields of psychology and psychiatry [16]. Furthermore, since various data-sharing platforms are siloed, re-use is currently difficult to measure systematically, preventing the evaluation of its benefits.

A call for action: towards policies and practices that maximize clinical trial value

These discouraging findings call for action in order to ensure that the ICMJE data-sharing policy will draw nearer to its goal of "creating an environment in which the sharing of de-identified individual participant data becomes the norm" [7]. Realistically, we recognize that the ICMJE cannot achieve this change alone without support and endorsement by other stakeholders. We call for the ICMJE to take the lead in charting a path towards policies and practices that maximize clinical trial value. This path could then lead to a cultural shift towards enhanced data sharing, perhaps supported by institutions, funders and others. While journals are the custodians of research articles, there appears to be little attention to the expressed desires of patients, surely equally important players in knowledge dissemination. We see an urgent need for data-sharing policies to be strengthened, adequately implemented and monitored. Secondly, easy-to-use technical infrastructures, administrative processes, and practice guidelines are needed for successful implementation of the different policies. Lastly, clinical trial data-sharing should be adequately identified, recognized as a behavior that increases research integrity, and therefore incentivized in line with the Hong Kong Principles for assessing researchers [17]. There is a need to reach a consensus on the best practices for data generators, curators and re-users in data sharing. Rewarding and recognizing adequately these best practices is expected to be paramount in increasing data sharing value. In addition, any incentives must pre-emptively consider how to diminish, rather than exacerbate, the inequities between developed and developing countries in generation and use of data [18].

A centralized approach towards monitoring of data-sharing is needed, where data-sharing dashboards would collect these data-sharing metrics (e.g. intention to share, data-sharing, data re-use) from journals, funders, and repositories, and then present it to the research community. Currently, this information is siloed (e.g. each data-sharing platform presents this information separately) and is not presented broken down by journal and by specific journal articles. Recent efforts have been made to monitor data-sharing, and other open science practices, in journal articles [19], and these tools (https://github.com/quest-bih/oddpub) are already used at the QUEST center for transforming biomedical research in Berlin, Germany. These initiatives need to be generalized and be included in ICMJE policy. The challenges identified, together with suggested changes to ICMJE policy and details of the necessary evaluations are listed in **Table 8**.

We argue that the current practice of journals listed as ICMJE-affiliated without committing to its policies undermines the value of the affiliation. A basic certification reflecting policy implementation could increase commitment. For example, the "TOP factor", an indicator

dedicated to assessing transparency, openness, and reproducibility (https://www.topfactor.org/), could provide a certification of this nature. Specifically, a TOP factor of 3 indicates that the policy includes both a requirement and a verification process for the correspondence of data with the findings reported in the paper. For this purpose, each journal could have a Reproducible Research Editor, like the *Biometrical journal* for instance, with specific infrastructures to submit data and analyze manuscripts provided on the journal's web-based submission platform. Beyond journal metrics, article-based indicators can also be used to explore enforcement of the policy. Funder-based metrics like the "good pharma score card" [20] could also help improve research transparency. Together, such initiatives can be seen as primary steps in incentivizing data sharing behaviors.

Currently the ICMJE policy only encourages data-sharing but does not guarantee it. A more binding policy to favor data deposition whenever ethically possible is needed. We believe that the policy should include adequate incentives for data-sharing, as part of hiring, promotion and tenure of researchers, together with reinforcement measures that journals can adopt in case of non-compliance with data-sharing requirements. Incentives and sanctions should be implemented and evaluated to see if intentions are achieved. It would be unrealistic to expect all journals to endorse the same incentives and the same sanctions. Moreover, it should not be taken for granted that any incentive and any sanction would work. Specific interventions can be piloted at the level of single journals or groups of journals that feel comfortable with implementing, and evaluating these policies. Interventions need to be evidence based. For instance, it has been suggested that awarding badges for data sharing could be an efficient incentive for data availability. Still, randomized evidence suggested that these tools may be ineffective in the area of biomedical science [21]. Even more challenging, the evidence gathered to inform the policy should not be limited to surrogate indicators such as data availability, but should also assess whether the data are really used and whether these re-uses have an impact in moving medical research forward faster, by exploring data-sharing benefits and its possible limitations, information that is currently lacking. To this end, tracking re-uses and the impact of re-uses could be a good starting point.

This agenda requires changes to the ICMJE policy itself and also coordinated efforts by various stakeholders such as researchers, journals, funders and institutions, as illustrated in **Table 9**. It implies joining forces in an observatory of clinical data-sharing practices with continuous monitoring of journal outputs and empirical evaluations to measure the value of the ICMJE data-sharing requirements. Greater consideration and rewarding of best practices in data sharing can help incentivize data generators, particularly those who work in low-income countries [18]. At a more global level, it will provide necessary feedback on the ICMJE data-sharing policy and could indicate any action that might be needed to increase the value of clinical trial data-sharing. Ultimately, our ethical obligation to clinical trial participants is to optimally use the data gathered to achieve improved clinical outcomes and thereby benefit human health.

Table 8: Some identified challenges, suggestions and evaluation components for the ICMJE data-sharing policy

Identified challenge	Suggested change to the ICMJE policy	Evaluation component
Poor implementation of the policy by ICMJE-affiliated journals.	To certify ICMJE-affiliated journals based on their implementation of the policy. This could be facilitated if journals have a reproducibility research editor.	Developing software to monitor journals' implementation of ICMJE policy, e.g. in line with the TOP factor developed by the Center for Open Science.
Suboptimal intention to share data by RCTs published in ICMJE-journals with a data-sharing policy for RCTs.	Policies should require data-sharing unless major obstacles exist.	Monitoring ICMJE-affiliated journals' enforcement of the policy by implementing software to check whether papers offer data-sharing, similar to that proposed by the Berlin QUEST center.
Suboptimal intention to share data by RCTs in clinical trial registration on databases such as clinical trials.gov for funders with a data-sharing policy for RCTs.	Policies should require the use of registries making intention to share data mandatory.	Monitoring compliance with funders/sponsors' policies by implementing software to check whether data-sharing plans offer data-sharing, and reporting of this information by funders/sponsors, e.g. Trial Tracker for clinical trial results, and the Good Pharma Scorecard (https://bioethicsinternational.org/good-pharma-scorecard/) for pharmaceutical firms.
"Data-sharing upon request" is not sufficient to ensure that data are shared.	Policies should favor data deposition when it is ethically possible. Policies should also outline more clearly the procedures that data requesters should follow and how journals can reinforce data-sharing in case of non-compliance with promises.	Monitoring data availability by implementing practical tests of the policy. Performing interventional studies to evaluate mechanisms of sanction and incentives.
Impact of clinical trial data-sharing is still insufficiently documented.	State explicitly that policy aiming to reform medical science needs to be evidence-based. Policy should be continuously informed and revised via a strong evaluation component.	Defining and testing best practices in clinical trial data-sharing to maximize clinical trial value. Prospectively monitoring the impact of data-sharing policies on the progress of medical research, using observational and interventional designs. This implies developing a tool to identify clinical trial data re-use and then to track the impact of re-uses. Portals are needed that collect this type of data from a wide range of sources (journals, funders, repositories…) since currently, all this information is siloed.

Table 9: Proposed actions for various stakeholders to ensure that the ICMJE policy meets the mark

Stakeholders	Proposed action
ICMJE	Should certify compliance, adopt more binding policies, and clarify when clinical trial data-sharing is required and ethically possible.
Journals	Should provide oversight with editorial screening (e.g. by a reproducible research editor) and software screening (e.g. by implementing an IT-infrastructure to verify data-sharing processes described in submitted data-sharing plans). Should embargo future publications from authors if they have not shared their data from previous manuscripts in their journal despite a promise to do so.
Funders/ institutions	Should monitor and reward data-sharing. Should provide technical/regulatory guidance for clinical trial data-sharing. Should implement Data Use and Access Committees (DUACs). Should withhold support from investigators not sharing data. Should support meta-research efforts that evaluate the impact of clinical trial data-sharing.
Researchers	Should commit to sharing data. Should engage in evaluating the impact of clinical trial data-sharing and provide the necessary feedback to improve the policy.

CHAPITRE 4 : Réanalyse d'un échantillon d'essais cliniques randomisés, disponibles sur les plateformes de partage de données

RESUME

Cette étude transversale a pour objectif d'explorer la reproductibilité inférentielle (c'est-à-dire que les données individuelles des patients sont disponibles et que des conclusions qualitativement similaires peuvent être tirées d'une réanalyse des essais originaux) d'ECR, pour lesquels les données sont disponibles sur quatre des principales plateformes de partage de données d'essais cliniques : Clinical Study Data Request, VIVLI, Project data sphere, Yale University Open Data Access.

Les demandes de données ont été effectuées pour un échantillon aléatoire de 62 études de phase III, sans distinction en termes de design, de comparateur ou de patients. Les essais dont la demande de donnée a été acceptée sont réanalysés, à l'aide du protocole et en aveugle des résultats originaux (publications et des rapports d'étude). Les résultats des réanalyses sont comparés à ceux des résultats principaux publiés en termes de conclusion, de p-value et d'effect size par deux chercheurs non impliqués dans la réanalyse. En cas de résultats contradictoires avec l'étude originale, il est prévu qu'un statisticien réanalysera les données de manière indépendante avant de conclure à un manque de reproductibilité inférentielle.

Nous présentons dans ce chapitre, le protocole accepté de principe puis l'ensemble des résultats préliminaires car l'étude est toujours en cours. Les résultats finaux seront présentés dans un article accepté de principe pour publication dans la revue Royal Society Open Science.

Les résultats préliminaires suggèrent un pourcentage d'accessibilité élevé des données d'essais cliniques via les plateformes de partage et une bonne reproductibilité inférentielle. Sur 21 essais réanalysés, 18 (85,7 % % [70,7 % ; 100 %]) étaient reproductibles.

STUDY PROTOCOL

Acknowledgments:

"This study, carried out under YODA Project # 2020-4454, used data obtained from the Yale University Open Data Access Project, which has an agreement with JANSSEN RESEARCH & DEVELOPMENT, L.L.C.. The interpretation and reporting of research using this data are solely the responsibility of the authors and does not necessarily represent the official views of the Yale University Open Data Access Project or JANSSEN RESEARCH & DEVELOPMENT, L.L.C.."

"This publication is based on research using data from data contributors AbbVie, Boehringer Ingelheim, Lilly, Pfizer, Roche, Takeda and UCB, that have been made available through Vivli, Inc. Vivli has not contributed to or approved, and Vivli, AbbVie, Boehringer Ingelheim, Lilly, Pfizer, Roche, Takeda and UCB, are not in any way responsible for, the contents of this publication."

Inferential reproducibility of therapeutic research: A registered report for a cross-sectional study of randomized controlled trials available on major data-sharing platforms.

Jeanne Gaba, Maximilian Siebert, Alain Renault, Bruno Laviolle, Clara Locher, David Moher, Florian Naudet.

Registered report accepté de Principe par la Royal Society Open Science.

Un registered report est un format de publication en deux phases : la première phase consiste à la soumission du protocole et à son évaluation par les pairs. La deuxième phase consiste à la publication des résultats de l'étude, à condition que l'étude soit réalisée conformément au protocole préalablement évalué et accepté suite à l'évaluation par les pairs (acceptation sous principe) (148).

Jeanne Gaba a participé à la conception de l'étude (design, rédaction du protocole), à l'extraction des données, à l'analyse des données, à l'interprétation des résultats et a rédigé l'ensemble de ces résultats préliminaires.

ABSTRACT

Randomized Controlled Trials (RCTs) are of major importance in providing information about health practices and policies. Ideally, the general public and scientists feel more confident when their methods and results can be reproduced. This registered report introduces a cross-sectional study aiming to explore inferential reproducibility (i.e. Individual Patient Data is available and qualitatively similar conclusions can be drawn from a re-analysis of the original trials) for RCTs, for which there is available data on major data-sharing platforms.

This study will include RCTs identified on 4 repositories (Clinical Study Data Request, VIVLI, Project data sphere and Yale University Open Data Access). Eligible RCTs will be phase III studies conducted in the field of therapeutics. 62 of these studies will be randomly sampled, ensuring a precision of ± 7.5% to estimate our primary outcome, i.e. the proportion of studies where the conclusions are reproduced (we hypothesize that more than 90 % of studies could be reproduced). One researcher will then retrieve the Individual Patient Data for these studies and other necessary documents for re-analysis by contacting the platforms and the study sponsors. For each study he will prepare a dossier containing the IPD, the protocol and information on the conduct of the study. A second researcher who will have no access to study reports (including publications) or analytical codes will use the dossier to run an independent re-analysis of each trial. All results from these re-analyses will be reported in terms of the conclusions, p-values, effect sizes and changes from the initial protocol in each study. Then a team of two researchers not involved in the re-analysis will compare results of the re-analysis with the published results of the trial. In case of conflicting results, a statistician will re-analyse the data independently before concluding to a lack of inferential reproducibility. Key issues that arose in the course of data requests and reanalysis will be qualitatively described.

This registered report is part of a wider project called "Reproducibility in Therapeutic Research", funded by the Agence Nationale de la Recherche, and a complementary registered report aims to explore the reproducibility of trials used for decision-making on Marketing Authorizations for new medicines in the European Medicine Agency.

BACKGROUND

Ideally, the public and scientists feel more confident when the methods and results of scientific experiments can be **reproduced** i.e. it is possible to achieve the same results and conclusions by performing the same procedures as accurately as possible, using the same data and tools as the original study (149). Performing **re-analyses** that successfully reproduce results, methods or conclusions helps build confidence in scientific evidence. However, there are growing concerns about findings that cannot be reproduced (150) (151). As a result, scientists have launched certain reproducibility initiatives. For example, in psychology, a collaborating team of several authors volunteered to **re-run studies in order to obtain the same results** with the methods used by the original researchers (**result reproducibility**). However the **results** were reproducible only for 39/100 experiments in this study (152). The same concerns have been expressed about biomedical research (153).

The existence and extent of reproducibility problems in the field of biomedical research is still unknown and few studies have attempted to answer the question. Results of a scoping review that we conducted to explore the impact of data sharing initiatives showed that studies whose purpose is data reuse are rarely intended for re-analysis (154). A recent investigation of data for 1622 new drugs submitted to China's Food and Drug Administration (CFDA) for registration concluded that 1308 (81%) of the applications should be withdrawn because they contained fabricated, flawed, or inadequate data from the clinical trials (155). Alongside, most re-analyses have been conducted for selected studies such as very controversial studies (e.g. Study 329, a well-known study on paroxetine in adolescent depression presenting the drug as safe and effective, while the re-analysis demonstrated a lack of efficacy, along with some serious safety issues).(156). An empirical analysis suggests that only a small number of re-analyses of RCTs have been published to date; of these, only a minority were conducted by entirely independent authors, showing the limitations in the verification of findings and the lack of available data or metadata. This analysis found that thirty-five per cent of published re-analyses yielded changes in findings that implied that the conclusions were meaningfully different from those of the original article as to which patients should be treated (157). In contrast, a systematic examination of studies published in the BMJ and PLOS Medicine (two journals with a strong data-sharing policy) found that the **reproducibility of analyses** was generally good, although not perfect (101). However, these re-analyses were performed using the very same analyses as the original papers (**method reproducibility**) and therefore may not necessarily have followed the best analytical standards.

One of the promises of clinical data-sharing is to facilitate the availability of data and thus to enable these re-analyses to be conducted. In line with a wider movement involving health authorities (158), the International Committee of Medical Journal Editors (ICMJE) encourages data-sharing (132). Numerous pharmaceutical companies have created mechanisms for investigators to access Individual Patient Data (IPD). Although more than 3000 trials have already been made available to investigators through open data platforms up to 2016, only 15.5% have been requested by a small number of researchers. Most proposals have focused on

non-pre-specified subgroups or predictors of response rather than on the validation of study results (159).

Nevertheless, attempts to **reproduce** medical studies (pre-clinical or clinical) are often costly and difficult to perform. This is especially true for randomized controlled trials (RCTs), although these studies are expensive and typically of major importance in providing information on health practices and policies. It is nonetheless possible, in a first approach, to explore whether qualitatively similar results and conclusions can be drawn from an independent re-analysis of RCT data (**inferential reproducibility**). This independent reanalysis is carried out in order to estimate **the reproducibility of the inference** (conclusions), which means that the objective is not necessarily to reproduce the same analytical methods (**reproducibility of the methods**) or the same numerical results (**reproducibility of the results**), but to see whether, using only the original study protocol and data, it would be possible to find a clinically meaningful equivalence between the reanalysis and the original analysis. As part of a global research program on Reproducibility in Therapeutic Research (ReiTheR, funded by the French National Research Agency (160)), we designed this cross-sectional study to assess the **inferential reproducibility** after reanalysis of a sample of RCTs registered on selected data-sharing platforms.

To give a clear and precise orientation to this paper, the terms used to refer to reproducibility have being defined (**Box 2)** following the lexicon provided by Goodman *et al*.(149), to avoid confusion(161).

Box 2: Definitions of terms, following Goodman *et al.* (149)

Reproducibility:

The ability to obtain the same results or observations through a new analysis using the same procedures as those used in the initial study.

Method reproducibility:

The ability to repeat the same analyses as the initial study with sufficient detail about the data and procedures.

Result reproducibility:

The ability to obtain the same results from a new study using the same procedures as far as possible as those of the initial study.

Inferential reproducibility:

The ability to obtain similar conclusions from a re-analysis of the original study.

METHODS

This is a registered report: the document will be submitted, and peer-reviewed before data collection and analysis. We believe that defining and registering the research question and protocol before any analyses could help to improve research transparency, quality and reproducibility. In addition, the protocol will be registered on the Open Science Framework (162) and will be made publicly available.

Eligibility criteria

Platforms

We will include operating data repositories/platforms identified in 1/ a review (163) conducted by Yolarx Consultants for the Wellcome Trust and 2/ a review of available repositories (164) that :

- are focused on clinical trial data;
- provide access to patient-level data from Phase III clinical studies;
- are not related to a specific disease;

Figure 8 shows the selection of data repositories included and **Table 10** their characteristics.

Table 10: Characteristics of selected data repositories

Repositories	Mission	Data type	Repository type	Funding	Ownership	Governance	Fees	Access	Access policy	Access procedure	Filters for quick Phase III studies searching	Number of available RCT datasets
The YODA project	To advocate the responsible sharing of clinical research data, open science, and research transparency	Clinical trials. Patient-level data.	Curated data.	Research grant through Yale from Johnson & Johnson, formerly funded by Medtronic, Inc	Yale University, Connecticut.	The Steering Committee provides guidance to the YODA Project, specifically in reference to developing processes for making clinical trial data available to external investigators, as well as processes	No fees.	No information.	No information.	**1-**YODA project review; **2-** Request for additional information or clarification if necessary; **3-** Due Diligence Assessment; **4-** External review; **5-** Decision	No	334

						for reviewing requests for these data.				regarding data access; **6-** Signature and submission of a Data Use Agreement by the requestor; **7-** Data availability.		
Clinical Study Data Request	CSDR seeks to be "the researcher-preferred and trusted" platform for responsible sharing of high-quality patient-level data for the purpose of facilitating innovative data-driven research	Clinical trials. Individual Patient data.	Curated data.	Consortium of clinical funders/sponsors.	No information.	No information.	No fees.	Researchers.	Researchers must sign a Data Sharing Agreement.	**1-** Submission of the research proposal and request for anonymized data; **2-** Decision regarding data access; **3-** Access to the data	Yes	3080

	leading to improvements in patient care									after the study sponsor receives the data sharing agreement;		
VIVLI	Vivli established a data sharing platform that includes an independent general access data repository that is available for searching for data from clinical trials conducted by researchers in academic,	Clinical Trials; Individual Patient Data; Metadata.	Platform of aggregated data.	Doris Duke Charitable foundation The Leona M. and Harry B. HELMSLEY Charity Trust Laura and John Arnold foundation Lyda Hill foundation PhRMA.	No information.	Board of directors.	Fees for sharing and archive data.	Researchers.	Users can search for studies, request data packages, and analyze data sets within a secure research environment.	**1-** Research team requests studies; **2-**Data request review; **3-** Signature of Data Use Agreement; **4-**Data contributor uploads data package;	Yes	4322

	industry, foundation and non-profit entities that can be hosted, shared and accessed								**5-** Research team begins analyses;		
Project data sphere	To provide one place where the research community can broadly share, integrate and analyze historical, patient-level data from academic and industry phase III cancer clinical trials	Clinical trial datasets from different depositors; Patient-level data.	Curated and standardized (CDISC-based) data.	Data Sphere project is supported by the members of the CEO Roundtable on Cancer Life Sciences Consortium through voluntary, in-kind contributions.	Project Data Sphere is an independent, not-for-profit initiative of the CEO Roundtable on Cancer Life Sciences Consortium.	Officers: President, 1st Vice President, Treasurer, Assistant Treasurer. The officers can call upon the Executive Committee, to advise on ethical and scientific matters.	No fees.	Researchers affiliated to life science companies, hospitals and institutions, as well as independent researchers.	All interested in gaining access will be directed to complete a user application and agree to the terms specified in the Online Services User Agreement. Once one has been granted access to the Data Sphere	**1-**Apply for data access; **2-**Data request review; **3-**Access to data if request accepted;	Yes	211

	platform as a registered user, the data will be available to you for one year. Users will be notified about the need to renew their annual application prior to the end of the term.	

Study eligibility

This cross-sectional study will include RCTs identified on the selected platforms, registered before randomization of the first participant in a WHO-approved registry such as clinicaltrials.gov, sharing their anonymized individual participant data (IPD). Eligible RCTs will 1/ be phase-III randomized studies (including phase II/III), 2/ include cluster, parallel trials and cross-over studies, 3/ include non-inferiority (and equivalence) designs and superiority designs, 4/ make no distinction in terms of patients, intervention, comparator or outcome, and 5/ be conducted in the field of therapeutics (i.e. with an objective of developing, evaluating or testing a drug, a medical device or equipment (165), a "talking therapy" or a combination therapy).

Furthermore, studies with no identified primary outcome will not be included but will be listed as non-evaluable studies. Qualitative studies will not be included.

Search strategies

Trials

If a list of all eligible RCTs cannot be extracted directly from the selected platform website, the platform personnel will be contacted in order to obtain a list of all RCTs meeting the inclusion criteria present on the platform. Sixty-two RCTs will be randomly selected among all the available studies across the platforms included, without stratification on the platform. Data access requests for these 62 RCTs will be made according to the access policies of the corresponding platforms.

Sample size calculation

Little data is available concerning the reproducibility of clinical trials. An empirical analysis estimated that 35% (13/37) of published re-analyses performed up to 2014 yielded changes in findings that implied conclusions different from those of the original article as to whether patients should be treated or not, or which patients should be treated (157). It is unlikely that published reanalyses in the past would be have been published if they had found the same results and had reached the same conclusions as the original analysis. Most reanalyses were performed by authors involved in the original trial and most assessed the effect of different analytical methods or a change in definition of results on the estimate of the trial effect. Therefore, the set of published reanalyses is more likely to report discrepant results and conclusions. The above-mentioned empirical analysis was based on a very selected sample and the observed estimate of different conclusions (35%) is probably overestimated. Given the limitations of this study and the fact that RCTs are highly codified and that it is unlikely that their analyses will be

distorted by more than 10 %, we certainly would not expect that 35% of the re-analyzes would lead to different conclusions.

In a more recent assessment (101), no differences in conclusions pertaining to treatment decisions were found after the re-analyses of 17 RCTs published in BMJ and PLOS Medicine, but errors were found in two, and one was not reproducible due to insufficient information in the Methods section. Importantly, none of these errors changed the conclusion (i.e. 100% of inferential reproducibility in this study). However, as explained in the introduction, this study used the same analysis as the original paper and may have overestimated the reproducibility of these studies.

Therefore, considering these two available studies, we anticipated that only 10% of the studies would lead to different conclusions (see paragraph "Procedure to explore reproducibility").

We calculated that a random sample of 62 RCTs has sufficient statistical power to achieve an expected precision of 7.5%. In addition, with a 95% confidence level, this sample size will ensure a precision of +/- 12% even if the percentage of reproducible studies (our main outcome) is around 50 % (the worst case for precision estimations). This random sample will be selected using R (166).

Trial document accessibility

For each RCT included, one reviewer (MS) will contact each platform, according to their specific procedures, to collect all of the following trial documents: 1) IPD, 2) data analysis plan document (also commonly known as a Statistical Analysis Plan (SAP), 3) analytical code, 4) study protocol and any time-stamped amendments, 5) all the following dates: date of the last visit of the last patient, date of database lock (if available) and date of study unblinding, 6) unpublished and/or published (scientific article) study reports. Trial registers will also be consulted to gather as much information as possible about the studies included.

Requests for data will be made according to the instructions on each included platform. Depending on the waiting period stipulated by each platform, two reminders will be sent in case of non-response (or after 4 weeks if no waiting period is mentioned by the platform). All necessary documents for the test will be cited in our data request. The documents obtained will be described in the data-sharing modalities (Table 12).

Should any of this information be missing, the reviewer will send a standardised email to the sponsor (**web appendix 1**), presenting the research project with a link to the pre-registered protocol on the Open Science Framework. If this information is requested, the data-sharing of IPD will be accepted in the form of SDTM, as created by CDISC (167).

Data extraction

The trial characteristics (described in **web appendix 2**) will be extracted from each included RCT as an Excel spreadsheet by two independent researchers (MS and FN or CL). In case of

disagreement, a third independent reviewer (FN or CL) will arbitrate. The data extraction sheet will be pilot-tested on 10 studies before validation.

Concerning the re-analysis, a first reviewer (MS, PhD Student) will collect the information and collate data for the re-analysis. More specifically, the reviewer will prepare a dossier with the following information for each study: 1/ the protocol, 2/ all amendments to the protocol (with their dates), 3/ all the following dates: date of the last visit of the last patient, date of database lock (if available) and date of study unblinding, and 4/ the IPD. In case of missing information, the study investigators/sponsors will be contacted.

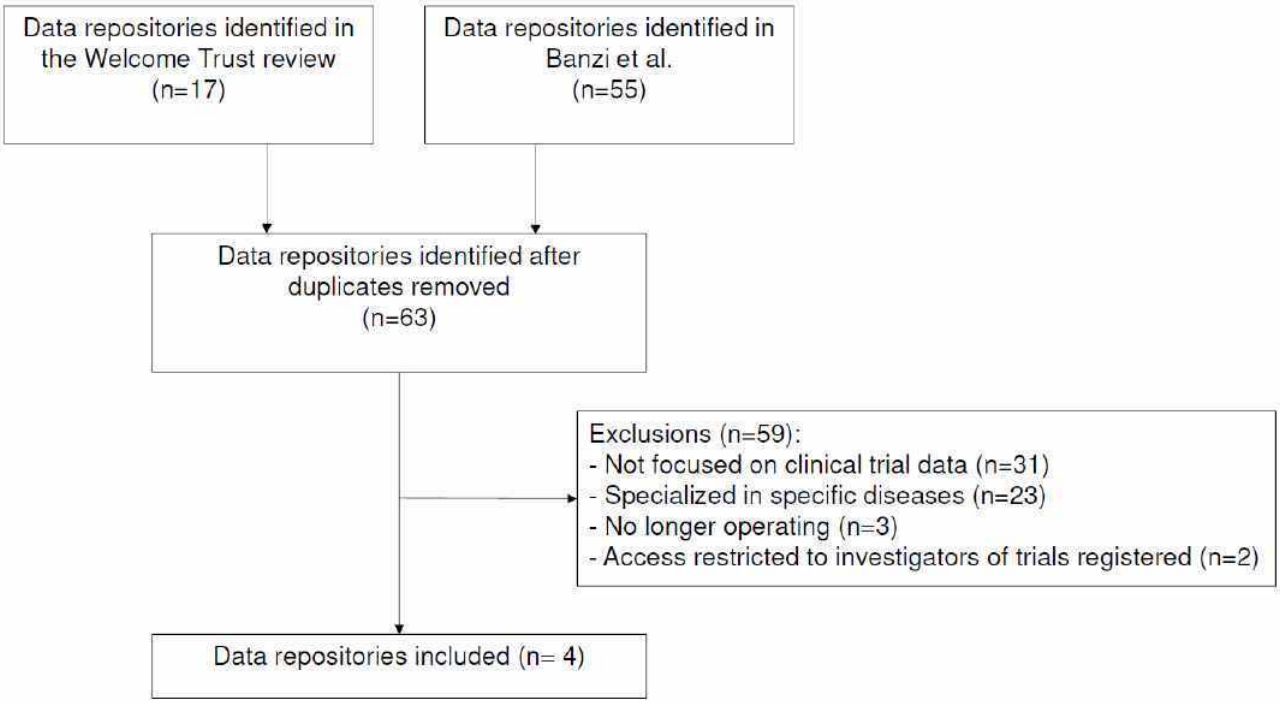


Figure 8: Selection of data repositories

Strategy for Re-analyses

Should IPD not be available one year after our initial request, the study will be considered as **inferentially non-reproducible** (primary outcome of our study). If sufficient information to reproduce the data is not available (e.g. protocol not available), we will use complete information from clinical trials registries in accordance with the ICH guidelines. If there is no protocol available and no registration of the trial, we will consider the study as **inferentially non-reproducible** and will describe the reasons for non-reproducibility.

On the basis of the dossier prepared by the first researcher, re-analyses of each primary outcome in the studies will be performed by a second researcher (JG, PhD student) who will have no access to study reports, journal publications, statistical analysis plans, or analytical codes, in order to ensure that the analysis is as blind as possible to the primary analysis. The researcher will have access to the relevant documents (data dictionary) provided by the platform to explain the raw data. In addition, this reviewer will be instructed not to seek out these documents or the published report.

For single-blind studies or open-label studies, analyses will be performed according to the version of the protocol at inclusion of the first patient, because outcome-switching is still a possibility to be looked for in these studies. For double-blind studies, all re-analyses will be based on the latest version of the protocol issued before database lock and unblinding. If this information is not available, the date of the last visit of the last patient will be used as a proxy. In case of missing information on these dates, the study investigators/sponsors will be contacted. In cases of outcome switching, meaning that a secondary outcome is considered as a primary outcome in the final analysis, both endpoints will be re-analyzed (to describe whether the outcome switching occurred because of an initial primary outcome that did not show statistical significance and in favor of a secondary outcome that did show significance).

Although statistical analysis is fairly simple in therapeutic research, in some cases re-analyses can involve difficult methodological choices. An independent senior statistician (AR) will be available to discuss any difficult aspect or choice in the analysis plan before the re-analysis, so as to choose the most consensual analyses (e.g. Intention-to-Treat population for a superiority trial).

While protocols specify the overall aims and general plan for analysis of a trial, they may or may not contain a SAP and it is not uncommon for a SAP to change substantially over the course of a study in response to unforeseen issues in the conduct and subsequent analysis of the study (168). If the SAP is an integral part of the protocol, it will be considered when planning the reanalysis. The protocol will be followed as planned. Should insufficient information concerning the main analysis be provided in the protocol, the best practices for clinical research will be used following the recommendations of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). If the original SAP was written after data collection (not included in the protocol), it will be taken into account only after the first reanalysis (this process will help to explore reasons for discrepancy in case of divergence of results).

All the information extracted by the second researcher for the reanalysis (on the dossier prepared by the first researcher) will be managed following these steps:

1- Extraction in the protocol.

2- Is the information present? If it is, questions 3. If not, replace the information according to the ICH guidelines and information in trial registries.

3- Is it adequately defined and well described following the reporting guidelines for interventional studies (SPIRIT/SPIRIT-PRO) implemented by the Equator Network? (e.g. for outcomes, check if the following are mentioned: Primary, secondary, and other outcomes, including the specific measurement variable (e.g. systolic blood pressure), metric analysis (e.g. change from baseline, final value, time to event), method of aggregation (e.g. median, proportion), and time points for each outcome. Explanation of the clinical relevance of the chosen efficacy and harm outcomes is strongly recommended).

If the response is no to question 3, the information is substandard.

Re-analyses will implement the following different steps: 1/ identification of the primary outcome (identification of outcome switching), 2/ definition of the analysis population, 3/ construction of the SAP, 4/ re-analysis of the primary outcome. Any change identified between the first version of the protocol and the version used for the re-analysis of the primary outcome will be tracked and described.

Table 11 describes how the ICH guidelines will be used to replace missing items, insufficient or substandard information in the documents provided by the platforms when developing the analysis plan for each study included. This analysis plan will be recorded on OSF for each study. Differences between the reanalysis SAP and the original study analysis plan will be also described.

		Information in the study documents	If present, is it substandard?	If not present, replace according to	Information used in the reanalysis
General information	Study title		-	-	
	Registration number		-	-	
	Protocol and amendments number		-	-	
	Name of the sponsor		-	-	
	Trial objectives (PICO)			-	
	Type of documents available		-	-	
Trial design	Design configuration			ICH E9, Point 3.1	
	Type of comparison			ICH E9, Point 3.3 ICH E10	
	Multicenter trial			ICH E9, Point 3.2	
	Primary outcomes			ICH E9	
	Sample size			ICH E9, point 3,4	
	Methods to minimize bias			ICH E9, point 2.3 ICH E10, point 1.2	
	Effect size			ICH E9, point 3.5	
	Confidence interval			ICH E9, point 5.5	
	Interim analysis			ICH E9, point 4.5	
	Analysis method			ICH E9, point 5	
	Handling missing data			ICH E9, point 5.3	
	Hypothesis testing			ICH E9, point 5.5	
	Statistical packages used for analysis			-	
	Protocol violations			ICH E9, point 2.3 ICH E6, point 6	
	Analysis sets			ICH E9, point 5.2	
Funders	Fundertype (commercial/non commercial)				
	Name				

Table 11: Example of a study analysis plan

Procedure to explore reproducibility

All results of these analyses will be reported in terms of 1/ binary conclusion (positive or negative), 2/ p-value, 3/ effect size (and details about the outcome) 4/ changes compared to the initial protocol. These results will be compared with results of the analyses reported in the study reports, and, if available, the publication reporting the primary results of the completed trial.

Because interpreting an RCT involves clinical expertise and cannot be reduced to solely quantitative factors, an in-depth discussion between two researchers not involved in the re-analysis (MS and FN), based on both quantitative and qualitative (clinical judgment) factors, will enable a decision on whether the changes in results described quantitatively could materialize into a change in conclusions. If these two reviewers judge that the conclusions are the same, the study will be considered **as inferentially reproduced**.

If these two researchers judge that the conclusions are not the same, then the researcher in charge of the analysis (JG) will be given the statistical analysis plan of the study and will be asked to list the differences in terms of analysis. If the analytical code is provided by the data-sharing platform, it will be also compared with the reanalysis code. If the researcher finds a discrepancy between the study data analysis plan and her own analysis plan, or between the study statistical code and her own statistical code, she will then correct this discrepancy in her analysis if justified (e.g. analysis population, use of covariates). An in-depth discussion between two researchers not involved in the re-analysis (MS and FN) will enable a decision to be made on whether the changes in results described quantitatively could materialize into a change in conclusions and whether the differences in terms of analytical plan are understandable and acceptable. If these two researchers judge that the conclusions are the same, the study will be considered as **inferentially reproduced with verification**.

If these two researchers judge that the conclusions are not the same or that the change in the analytical plan is neither justified nor desirable, then a senior statistician will perform his own re-analysis using the dossier initially prepared by the first researcher (researcher not involved in the reanalyses). Then a last in-depth discussion between two researchers not involved in the re-analysis (MS and FN) based on the senior statistician's re-analysis will enable a decision on whether the changes in results described quantitatively could materialize into a change in conclusions. If these two researchers judge that the conclusions are the same, the study will be considered as **inferentially reproduced with verification**, otherwise, the results will be considered as **inferentially not reproduced**. This process is described in **figure 9**.

The two reviewers involved in the reproducibility assessment will follow the steps shown in **Figure 10** to assess the similarity of the conclusions: first, they will compare the statistical significance using the p-values. If they differ, the result will be considered as not reproducible. If they do not differ, the reviewers will qualitatively compare effect sizes and their respective 95% CIs. In case of a difference of +/- 0.10 points in point estimates (expressed as standardized mean differences), the difference will be discussed with a clinician in order to assess its clinical significance.

Should the study be considered as not inferentially reproduced, the investigators/sponsors of the study will be contacted to discuss the discrepancy. This step will be performed after the

evaluation of all the discrepancies between the re-analyses and the analyses reported in the study documents (protocol, SAP, statistical code, publication). Although the detection of errors is not part of the objectives of this study, errors can constitute a reason for the lack of inferential reproducibility. A clinically significant difference between the original results and those of the reanalysis can be due to variation in methodology caused by poor specification in the documentation that led to either an ICH default different from what was actually used or a different implementation choice deemed justifiable by the reanalysis team.

Investigators or corresponding authors will be contacted by e-mail (including sponsors via copy) to discuss the non-reproducibility of the studies, notifying the differences found. If there is no response after 3 reminders (one per week over 3 weeks) to emails, we will consider that we have not received any response for the trial concerned.

Outcomes

As a primary outcome we report the proportion of trials in our cohort that were reproducible on the basis of the conditions and categories described in the methods. For non-replications, discrepancies that arise will be described quantitatively in terms of the differences in p-value and effect size. As a secondary outcome, we will qualitatively describe key issues that arose in the course of data requests and reanalysis, including any application to investigators for further information or discussion on non-replication.

The modalities of data-sharing (101) listed in **table 12** will be also described.

Type of data sharing	Accessibility of data: - Upon request by e-mail (see appendix) - Upon request on a specific website - Upon request on a specific register - Available on a public register - Other (specify)
Time allowed for collecting the data	- Time in days
Reason for non-availability if data was not shared	- Privacy concerns - Technical issues - Non-willingness to engage in sharing data - No data-sharing one year after the request - Other (specify)
De-identification of data	- Name (YES/ NO) - Birth date (YES/ NO) - Address (YES/ NO)
Type of data shared	- Analysable (e.g. AdAM) - Edited/cleaned (e.g. SDTM) - Computerised (e.g. CDASH)
Type of documents received	- Analytical code - Protocol - IPD - Other (specify)

Table 12: Modalities of data-sharing described after analysis

Data analysis

We will perform a descriptive analysis of the characteristics of the studies included (the description will be given for each platform). This will include counts, percentages and their associated 95% confidence intervals (CIs).

Effect estimates in the different studies will be expressed as standardized mean differences (SMDs) and their associated 95% confidence intervals (CIs). For binary outcomes, odds ratios and their 95% CIs will be calculated and converted into standardised mean differences (169). We will plot the effect estimates (and their 95% CIs) observed in the re-analyses against the effect estimates (and their 95% CIs) observed in the initial analyses. These results will be detailed for each platform.

All analyses will be performed using the R open-source statistical software (R Development Core Team) (166). The analytical code will be made public on the Open Science Framework (162) as well as a file summarizing the procedure to retrieve all data-sets.

In case of a divergent re-analysis (confirmed by a second re-analysis), we will advise the authors (and/or sponsors of the trial). Should exchanges with the authors prove impossible or not offer enough information to explain the reason for non-reproducibility, we will then inform the editors of the journals where the findings were published and/or the health authority in charge of the approval. We will first publish our results as a research letter, and we will subsequently run a complete re-analysis of the study, which we will then publish.

To further enhance our study, our results will be checked by comparison with another reproducibility project in the ReiTheR program submitted as a registered report. This second study involves a similar method to study the reproducibility of pivotal trials assessed by the European Public Assessment Report (EPARs), for new authorized human medications and biosimilars approved by the European Medicines Agency (EMA).

Risks for study completion and factors mitigating that risk

The blinding of the reviewer may not be certain all the time, as results from clinical trials can be found incidentally. To minimise this risk, the analyser (JG) will register his statistical analysis plan for each study on the Open Science Framework before conducting the analysis.

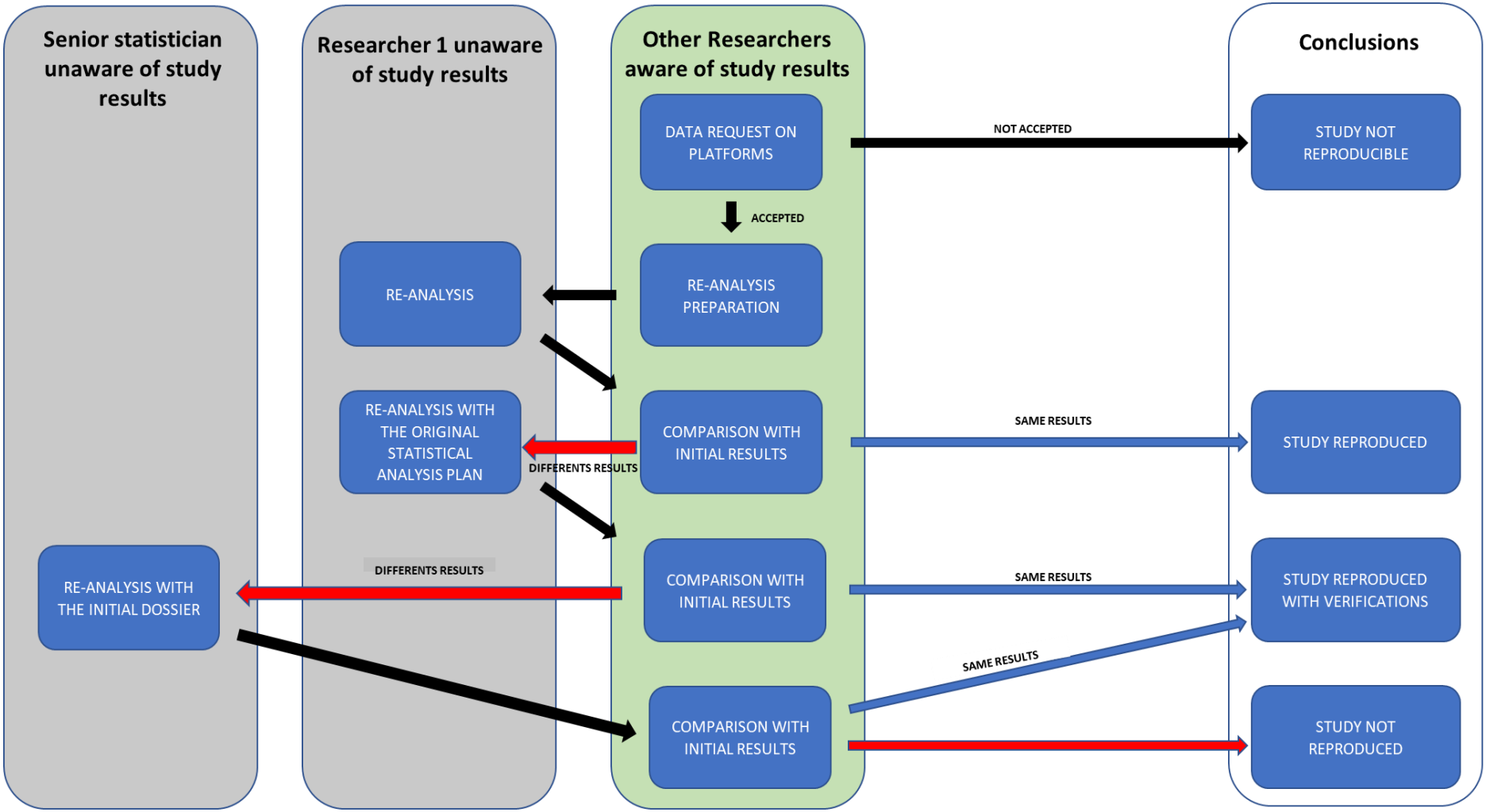


Figure 9: Procedure to explore reproducibility

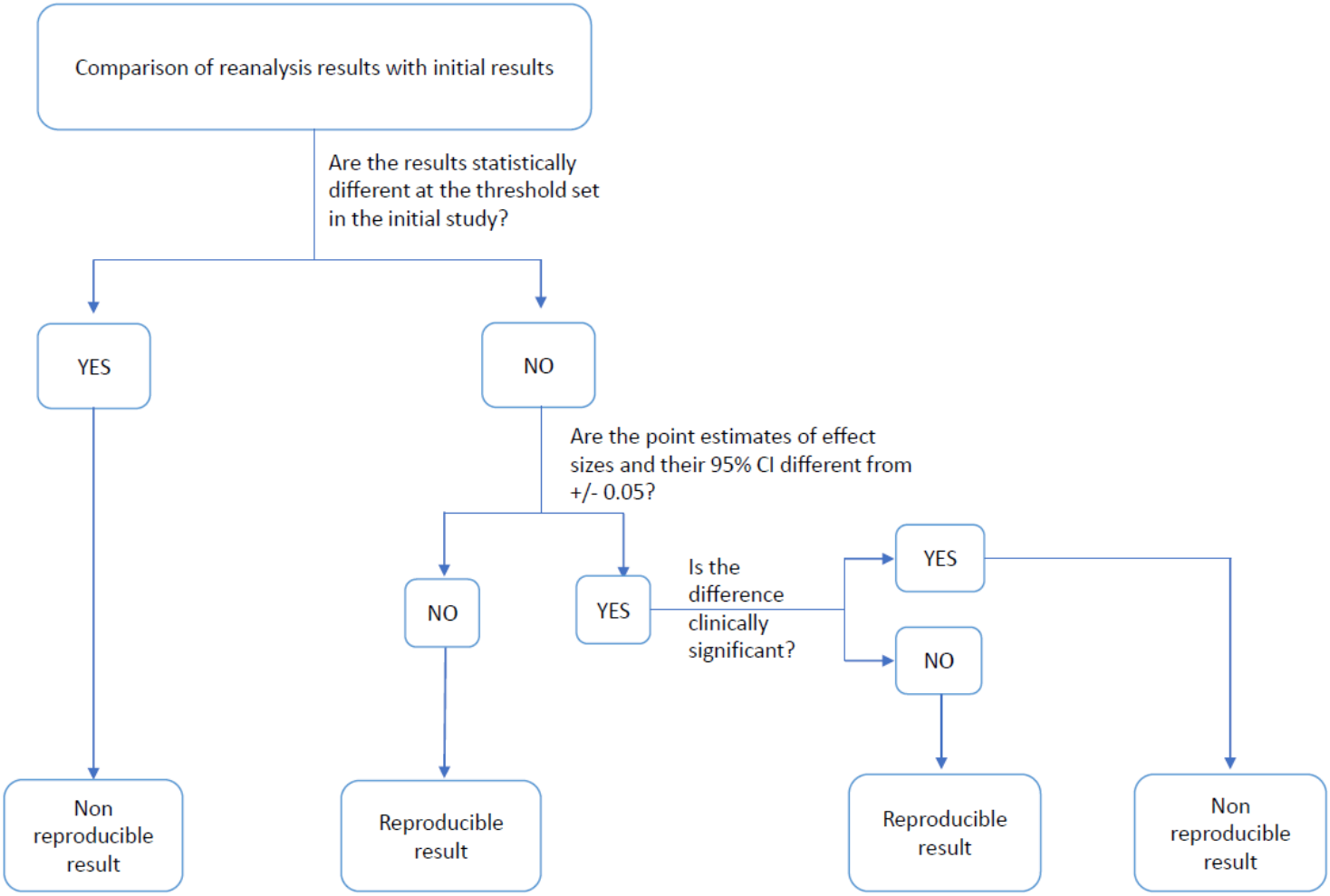


Figure 10: Reproducibility assessment

PRELIMINARY RESULTS

Change to the initial protocol

During the drafting of the protocol for our study, we have already identified the impact that the short duration of the thesis project could have on data accessibility. We then set a deadline of one year to obtain the data. In reality, the full dataset was not obtained within this set timeframe, due to the lengthy data request process, delays caused by a particular period of Covid-19 crisis and the novelty of clinical trials reanalysis in our research unit which entailed additional administrative procedures.

As the study has not yet been completed, we present below the provisional results, concerning the data which have been received and reanalyzed within the time limit imposed by the thesis project. The results relied on the completed data will be presented in the final article, in-principle accepted for submission in the Royal Society Open Science. The submission due for the final article is 8th December 2023.

Because verification by a senior statistician in case of different results between the conclusions of the original study and the conclusions of the reanalysis has not yet been carried out, we did not assess inferential reproducibility for reanalyzed studies that required a verification by a statistician. This change was made only concerning these preliminary results and will not affect the final results of the study.

Study selection and data availability

Figure 11 and **12** details the selection of included studies.

The breakdown of studies included by platform is as follows: 33 (53.2%) studies on Vivli, 22 (35.5%) on CSDR, 6 (9.7%) on YODA and 1 (1.6%) on Project Data Sphere.

The data access requests were sent to the platforms concerned between September 15, 2020 and September 23, 2020. The procedure for requesting data on the platforms was generally done as follows: 1/ Creation of an account on the platform; 2/ submission of the data request; 2/ Review of the research proposal (verification of the information provided, examination and validation of the research proposal); 3/ once the request was accepted, the data use agreement had to be signed before access to data through a remote environment. **Table 13** shows data accessibility and contains data request dates by platform.

Data sharing platform	First request date	Data access date	Number of studies' data requested	Number of reanalyzed studies	Number of Data Request Denied	Remains to be reanalyzed
Vivli	21/09/2020	01/09/2021	31	13	3	15
BioLINCC	18/09/2020	09/03/2021	2	2	0	0
YODA	15/09/2020	26/03/2021	6	6	0	0
CSDR	23/09/2020	-	22	0	3	19
Project Data sphere	15/09/2020	26/01/2021	1	0	0	0
			62	**21**	**6**	**34**

Tableau 13 : Data accessibility

The Project Data Sphere data request was the first to be accepted on January 26, 2021. This request concerns only one study, which was ultimately excluded because it did not meet the eligibility criteria for our analysis. Exploration of the IPD showed that it was included by error and therefore this study was not reanalyzed despite accessing the data. It was replaced by the next study in our randomisation list.

Data requests are still ongoing for studies available on CSDR on 14/09/2022. This is due to delays on our side related with institutional agreements.

The data request was denied for 6/62 studies, including 3 on Vivli, 2 on CSDR. Regarding the last study, the request for data was made on CSDR, which replied that the sponsor GSK no longer held the data, because the product (a vaccine) had been sold to Pfizer. When we asked Pfizer, through a new request on Vivli, the response was: "*we do not have individual subject data*".

The reason for rejection for one study on Vivli was that no efficacy analysis was performed because the study was terminated prematurely. The two last studies had the same sponsor, which express concerns about our ability to reproduce their studies and added that the primary data would add complexity to the reproducibility analysis. Additionally, they argued that the original Statistical Analysis Plan was not requested (it was actually requested) and that this would have a potential impact on reproducibility. Below the received notification:

"*SMEs demonstrated concerns regarding reproducibility of the analysis since there is no SAP provided. Another limitation would be the primary outcome data (NRI) which would add more complexity to the analysis reproducibility. Original SAPs have not been requested (as the intention is not to use them), so this might also potentially impact reproducibility*."

For the two studies on CSDR, the reasons for not sharing data, giving by the same sponsor were as follow: "*Agreement to share clinical data has not been gained with a co-development partner. Furthermore, the proposal does not address an unanswered medical question, it is the responsibility of Health Authorities to confirm the results of studies when considered appropriate".*

On these preliminary results 33.9% (21/62) of the included studies were reanalyzed by a first researcher, including 45.5% (15/33) of the included studies identified on Vivli, 100% of the included studies identified on YODA (6/6) and 0% (0/22) included studies identified on CSDR.

The data was accessible via a secure working environment, provided by the platform, except for 2 studies identified on Vivli, for which the data request was made via BioLincc. The data provided by BioLincc was downloaded and analyzed on our password-secured computer.

Study characteristics and Reproducibility

All reanalyzed studies were Phase 3 studies and only two studies (2/21) have noncommercial funders. For the 21 studies, we identified 24 distinct primary outcomes that were all reanalyzed, all resulting in 39 comparisons.

3 studies out of 21 are pending verification by a second statistician before concluding on their inferential reproducibility. For those 3 studies that needs verification by a senior statistician, two were not reproduced after verification with the statistical analysis plan. For one, the researcher in charge of the reanalysis did not found enough information to re-built the outcome variable. Data dictionary and the statistical analysis plan were missing and were asked to the promotor. We are still waiting for an adequate response. For the second study, results were not reproduced for all comparison groups. For the third study that needs a verification, the

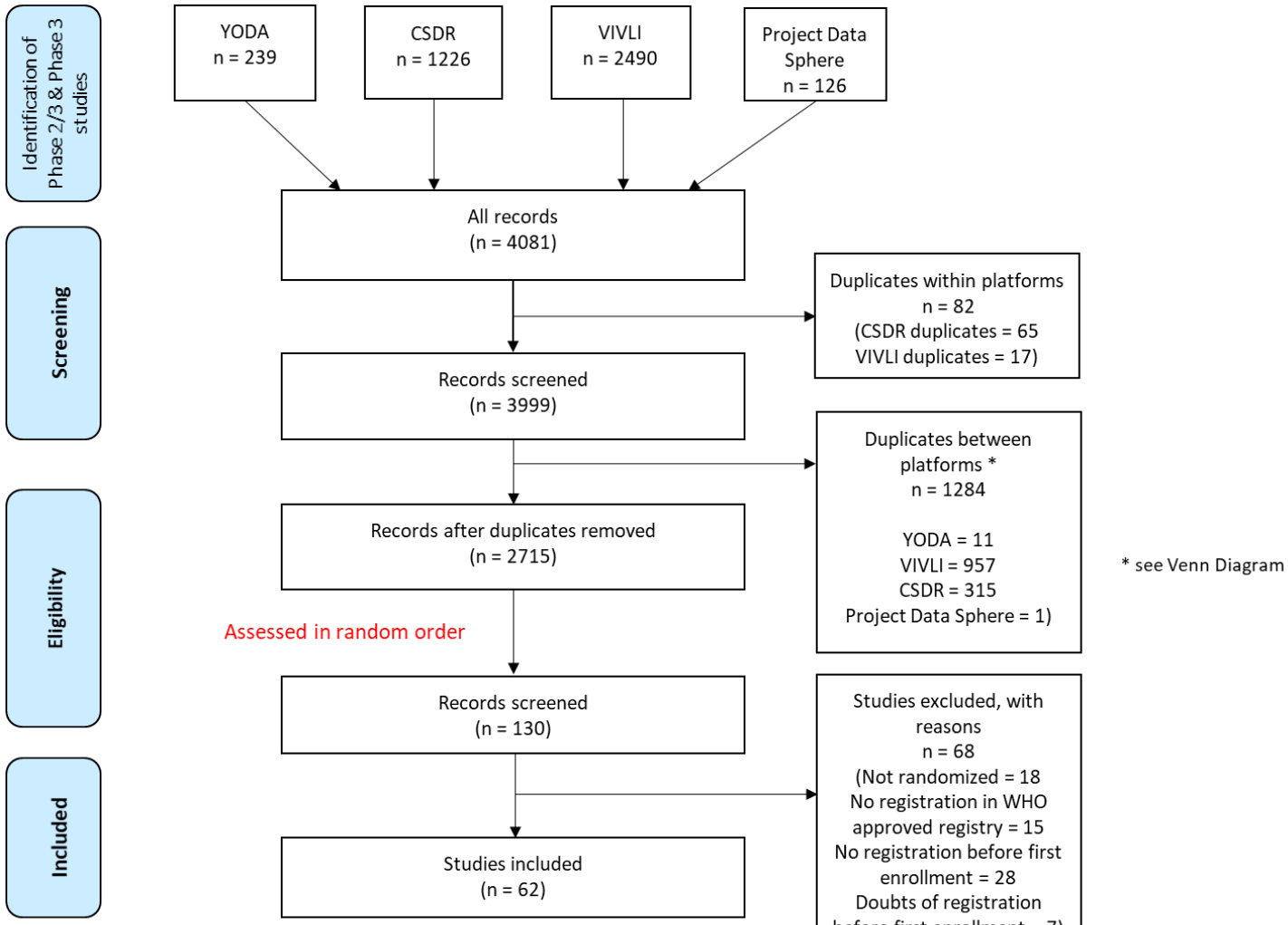
conclusion was reproduced, but there was spin in the publication; the study report and the publications show slightly different results.

At this stage 18 out of 21 studies 85.7% % [70.7 %; 100%] were reproducible and this number may increase after the second re-analysis. Characteristics of these studies, with reproducibility conclusion are presented in **Table 14**. All the outcomes for these studies were reproduced.

The reanalysis results and the original results reported in published article (**Figure 13**) and in the study report (**Figure 14**) were compared in term of standardized mean difference (Cohen's d).

Among those 18 studies, 16 were inferentially reproduced and 2 were inferentially reproduced with verification. For all these reanalyzed studies, we found no change in the primary outcome from the first version of the protocol. There was a spin in one reproduced study due to results that should not have been reported due to hierarchical testing.

Figure 11: Selection of included studies



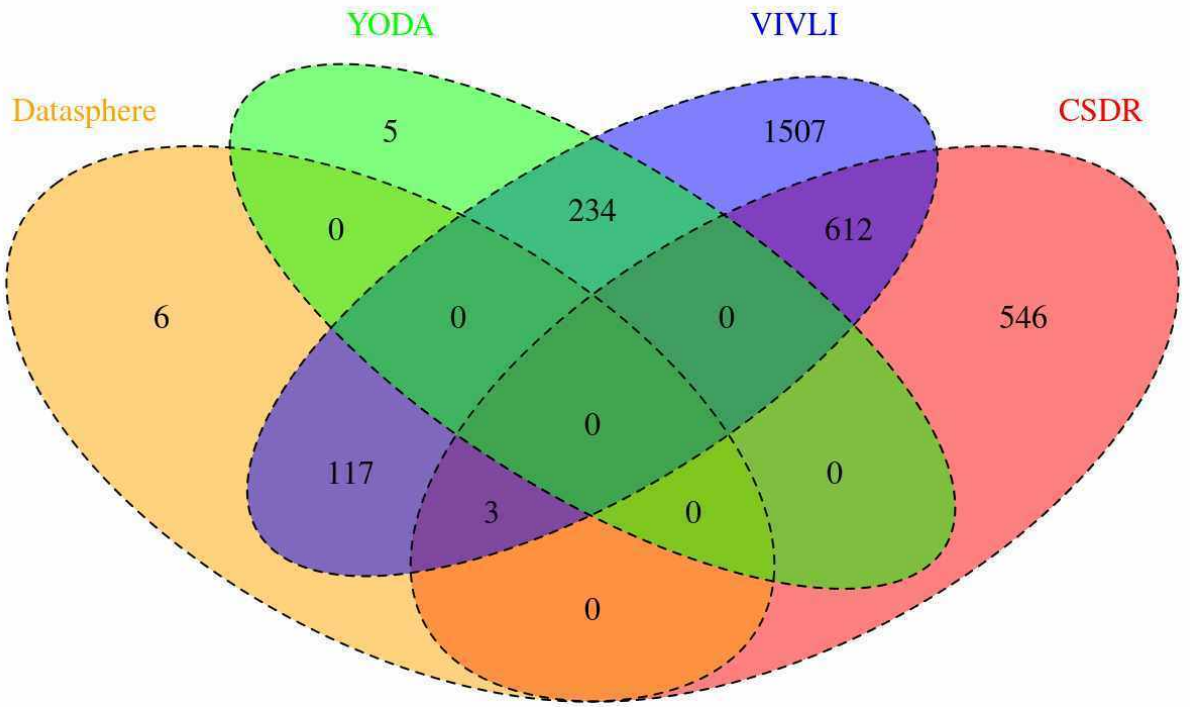


Figure 12: Venn Diagram representing the number of available studies on each platform

Table 14: Characteristics of all reproduced studies (the studies pending verifications are not displayed at this step as. They me be finnaly considered as reproduced depending on the second statistician independent re-analyses)

VIVLI/ BIOLINCC								
Reanalysis conclusion	**Clinicaltrial.gov ID**	**Title**	**Design**	**Outcome (Treatment or intervention comparison)**	**Statistical analysis method**	**Number of participants**	**Type of funder/ Funder or promotor name**	**Type of data and documents received**
Reproduced	NCT00883948	Early Versus Delayed Enteral Feeding to Treat People with Acute Lung Injury or Acute Respiratory Distress Syndrome (The EDEN Study)	Phase 3, Randomized, Multi-center, prospective, controlled trial	Ventilator-Free Days to study day 28 (full-calorie enteral feeds VS initial full-calorie feeds in patients with Acute Lung Injury or Acute Respiratory Distress Syndrome)	A three-way analysis of variance	ITT analysis set N=1000	Non-commercial/ The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome	IPD, protocol, data dictionary
Reproduced	NCT02066129	Step-up Yellow Zone Inhaled Corticosteroids to Prevent Exacerbations	Phase 3, Multi-center, prospective, randomized, double-blinded, controlled clinical trial	The rate of severe exacerbations treated with oral corticosteroids (1*ICS VS 5*ICS) *ICS: Inhaled corticosteroids*	Negative binomial regression		Non-commercial/ Milton S. Hershey Medical Center	IPD, protocol, date of the last visit of the last patient, data dictionary

YODA								
Reanalysis conclusion	**Clinicaltrial.gov ID**	**Title**	**Design**	**Outcome (Treatment or intervention comparison)**	**Statistical analysis method**	**Number of participants**	**Type of funder/ Funder or promotor name**	**Type of data and documents received**
Reproduced	NCT00086320	A Randomized, Double-blind, Placebo-controlled, Parallel-group Study With an Open-label Extension Evaluating Paliperidone Extended Release Tablets in the Prevention of Recurrence in Subjects With Schizophrenia	Phase 3, randomized, double-blind, placebo controlled, parallel-group study	Time to first recurrence during the double-blind phase (Placebo VS Paliperdone)	Survival analysis model	ITT analysis set N=205	Commercial/ Janssen-Cilag	Protocol, IPD, Data dictionary, CSR
Reproduced	NCT00518323	A Randomized, Multicenter, Double-Blind, Weight-Based, Fixed-Dose, Parallel-Group, Placebo-Controlled Study of the Efficacy and Safety of Extended Release Paliperidone for the Treatment of Schizophrenia in Adolescent Subjects, 12 to 17 Years of Age	Phase 3, randomized, multi-center, double-blind	Change in PANSS (Positive and Negative Syndrome Scale) total score from baseline visit to the last post-randomization assessment (3 treatment* groups VS Placebo) * *Low dose paliperidone, Medium dose paliperidone, High dose palideridone*	Analysis of co-variance	ITT analysis set N=201	Commercial/ Janssen-Cilag	Protocol, IPD, Data dictionary

Reproduced	NCT00309699	A Randomized, Double-Blind, Active- and Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy and Safety of Flexibly-Dosed, Extended-Release Paliperidone Compared With Flexibly-Dosed Quetiapine and Placebo in the Treatment of Acute Manic and Mixed Episodes Associated With Bipolar I Disorder	Phase 3, randomized, multi-center, double-blind	The change from baseline in total YMRS (Young Mania Rating Scale) score at the end of the double blind, acute treatment phase (Placebo VS Paliperidone)	Analysis of covariance	ITT population: Randomized N=493 Modified ITT N=487	Commercial/ Johnson&Johnson	Protocol, IPD, Data dictionary, CSR, SAP, CRF
Reproduced	NCT00973479	A Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Golimumab, an Anti-TNFalpha Monoclonal Antibody, Administered Intravenously, in Patients With Active Rheumatoid Arthritis Despite Methotrexate Therapy	Phase 3, Multicenter, randomized, double-blind, placebo controlled	The proportion of subjects with an ACR* 20 response at Week 14 (IV golimumab 2 mg/kg + MTX* VS and IV placebo + MTX*) **ACR20: American College of Rheumatology 20% improvement criteria* **MTX: Methotrexate*	Chi square test	ITT Population N=592	Commercial/ Janssen Research and Development	Protocol, IPD, Data dictionary, CSR

VIVLI								
Reanalysis conclusion	**Clinicaltrial.gov ID**	**Title**	**Design**	**Outcome (Treatment or intervention comparison)**	**Statistical analysis method**	**Analysis Population size**	**Type of funder/ Funder or promotor name**	**Type of data and documents received**
Reproduced	NCT 00105989	Duloxetine Versus Placebo in the Prevention of Recurrence of Major Depressive Disorder	Phase 3, randomized, double-blind, placebo controlled, parallel-group study	Time to recurrence (Placebo VS Duloxetine)	Survival analysis model	ITT analysis set N=288	Commercial/ Lilly and company	Protocol, IPD, Data dictionary, CSR, SAP analysis
Reproduced	NCT 00387088	A Randomised, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess Long Term (one year) Efficacy and Safety Study of Tiotropium Inhalation Solution 5µg (2 puffs of 2.5µg) Delivered by the Respimat Inhaler in Patients with Chronic Obstructive Pulmonary Disease (COPD)	Phase 3, randomized, double-blind, placebo controlled, parallel-group design study	2 co primary endpoints: (1) Change from baseline in trough FEV1 (2) Time to First Chronic Obstructive Pulmonary Disease (COPD) Exacerbation (Placebo VS Tiotropium)	Analysis of Covariance for outcome 1 Survival analysis for outcome 2	FAS analysis set N= 389 Modified FAS N=3856	Commercial/ Boehringer Ingelheim	Protocol, IPD, Data dictionary, CSR, SAP

Reproduced with verification	NCT 00621140	A Randomised, Double-blind, Placebo-controled Parallel Group Efficacy and Safety Study of BI 1356 (5 mg Administered Orally Once Daily) Over 24 Weeks, in Drug Naive or Previously Treated (6 Weeks Washout) Type 2 Diabetic Patients With Insufficient Glycemic Control	Phase 3, randomized, double-blind, placebo- controlled, parallel-group comparison	The change from baseline in HbA 1c (HbAc1* after 24 weeks of treatment) (BI 1356 VS Placebo) *HbAc1: hemoglobin A1C	Analysis of Covariance	Full analysis set N=496	Commercial/ Boehringer Ingelheim	Protocol, IPD, Data dictionary, CSR
Reproduced	NCT 00782210	Randomised, Double-blind, Placebo-controlled, Parallel Group Study to Assess the Efficacy and Safety of 48 Weeks of Once Daily Treatment of Orally Inhaled BI 1744 CL (5 mcg [2 Actuations of 2.5 mcg] and 10 mcg [2 Actuations of 5 mcg]) Delivered by the Respimat® Inhaler, in Patients with Chronic Obstructive Pulmonary Disease (COPD)	Phase 3, randomized, double-blind, placebo- controlled, parallel-group design	2 co-primary endpoints: 1- FEV1 AUC* 0-3h response 2-trough FEV1* response (2 treatment* groups VS Placebo) * *Low dose BI 1744, High dose BI 1744* **FEV1: Forced Expiratory Volume in 1 Second* *AUC* 0-3h: Area Under Curve 0-3 h	Restricted maximum likelihood (REML)- based repeated measures approach	Full analysis set N=620	Commercial/ Boehringer Ingelheim	Protocol, IPD, Data dictionary, CSR
Reproduced	NCT 00798161		Phase 3,			Full analysis set	Commercial/	

		A Phase III Randomised, Double-blind, Placebo-controlled Parallel Group Study to Compare the Efficacy and Safety of Twice Daily Administration of the Free Combination of BI 1356 2.5 mg + Metformin 500 mg, or of BI 1356 2.5 mg + Metformin 1000 mg, With the Individual Components of Metformin (500 mg or 1000 mg Twice Daily), and BI 1356 (5.0 mg Once Daily) Over 24 Weeks in Drug Naive or Previously Treated (4 Weeks Wash-out and 2 Weeks Placebo run-in) Type 2 Diabetic Patients With Insufficient Glycaemic Control	Randomised, Double-blind, Placebo-controlled Parallel Group	The change from baseline in HbA1c after 24 weeks of treatment 4 treatments groups: 1- Linagliptin 2.5 mg +metformin 1000mg, 2- metformin 1000mg, 3- Linagliptin 2.5 mg +metformin 500mg, 4- metformin 500mg, 5- Linagliptin 5 mg,	Analysis of Covariance	N= 756	Boehringer Ingelheim	Protocol, IPD, Data dictionary
Reproduced	NCT 01194414	A Randomized, Double-blind, Parallel Group Study of the Safety and Effect on Clinical Outcome of Tocilizumab SC Versus Tocilizumab IV, in	Phase 3, Randomized, double blind, active controlled, parallel group comparison	The proportion of patients achieving an ACR 20 response at Week 24	Proportions test Logistic regression for multiple variable and interaction testing	Per protocol population N=1127	Commercial/ Hoffmann-La Roche	Protocol, IPD, data dictionary

		Combination With Traditional Disease Modifying Anti-rheumatic Drugs (DMARDs), in Patients With Moderate to Severe Active Rheumatoid Arthritis		(2 groups of treatment: TCZ* 162 mg SC VS TCZ* 8mg/kg IV) *TCZ: Tocilizumab				
Reproduced	NCT 01215097	A Randomized, Double-blind, Placebo-controlled Parallel Group Efficacy and Safety Study of BI 1356 Over 24 Weeks in T2D Patients with Insufficient Glycaemic Control Despite Metformin Therapy	Phase 3, Randomized, double blind, placebo controlled, parallel group comparison	The change from baseline in HbA1c (HbA1c after 24 weeks of treatment) in all patients with baseline and at least one post baseline measurement. (Placebo VS Linagliptin (BI 1356 5 mg))	Analysis of covariance	Full analysis set N=300	Commercial/ Boehringer Ingelheim	Protocol, IPD, Data dictionary
Reproduced	NCT 01468233	A Phase 3 Multicenter Study of the Safety and Efficacy of Adalimumab in Subjects with Moderate to Severe Hidradenitis Suppurativa - PIONEER II	Phase 3, Randomized, Double-blind, Placebo-controlled Parallel	The proportion of subjects achieving HiSCR* at Week 12 (Placebo VS Adalimumab) *HiSCR: Hidradenitis Suppurativa Clinical Response	Stratified CMH test	ITT analysis N=326 Per protocol N=302	Commercial/ Abbvie	Protocol, IPD, data dictionary
Reproduced with verification	NCT 01634139	A Randomised, Double-blind, Placebo-controlled, Parallel-group Trial	Phase 3, Randomised, Double-blind,	The peak FEV1 response within 3h post dosing (FEV1 peak 0-3h response)	REML-based mixed model repeated measures (MMRM)	Full analysis set N=401	Commercial/ Boehringer Ingelheim	IPD, protocol, data dictionary

		to Evaluate Efficacy and Safety of Tiotropium Inhalation Solution (2.5 mcg and 5 mcg) Delivered Via Respimat® Inhaler Once Daily in the Evening Over 48 Weeks in Children (6 to 11 Years Old) With Moderate Persistent Asthma	Parallel Assignment, Interventional	determined at the end of the 24 weeks treatment period. 3 treatment groups: Tiotropium 5µg Tiotropium 2.5µg Placebo				
Reproduced **Spin because should not have been reported due to hierarchical testing**	NCT 02164864	A Prospective Randomised, Open Label, Blinded Endpoint (PROBE) Study to Evaluate DUAL Antithrombotic Therapy with Dabigatran Etexilate (110mg and 150mg b.i.d.) Plus Clopidogrel or Ticagrelor vs. Triple Therapy Strategy With Warfarin (INR 2.0 - 3.0) Plus Clopidogrel or Ticagrelor and Aspirin in Patients With Non Valvular Atrial Fibrillation (NVAF) That Have Undergone a Percutaneous Coronary Intervention (PCI) With Stenting	Phase 3, prospective, randomized, open label, blinded endpoint, active comparator trial	There are no primary efficacy endpoints. The primary endpoint for this trial is a safety endpoint. The primary endpoint is time to first ISTH major or clinically relevant non-major bleeding event 3 treatment groups : 110mg DE-DAT 150mg DE-DAT warfarin-TAT	Stratified Cox proportional hazards regression	Full analysis set N= 2725 Modified FAS N= 2533	Commercial/ Boehringer Ingelheim	Protocol, IPD, Data dictionary

Reproduced	NCT 02314117	A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of Capecitabine and Cisplatin with or Without Ramucirumab as First-line Therapy in Patients With Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma (RAINFALL)	Phase 3, randomized, double-blind, placebo- controlled, parallel assignement	Progression-free Survival (PFS) 2 comparison groups: Ramucirumab + capecitabine + cisplatin and Placebo + capecitabine + cisplatin	Survival analysis model Stratified Cox regression model	Full analysis set N=645	Commercial/ Eli Lilly and Company	Protocol, IPD, Data dictionary, CSR
Reproduced	NCT 00558428	An Eight-week Randomized, 4-arm, Double-blind Study to Compare the Efficacy and Safety of Combinations of Telmisartan 40mg + Amlodipine 5mg Versus Telmisartan 80mg + Amlodipine 5mg Versus Amlodipine 5mg Versus Amlodipine 10mg Monotherapy in Patients With Hypertension Who Fail to Respond Adequately to Treatment With Amlodipine 5mg Monotherapy	Phase 3, randomized, double-blind, controlled, parallel-group design study	2 co-primary endpoints are: - The change from baseline in seated trough (i.e. at 24 hours after last dose) DBP after eight weeks of treatment or at last trough observation during the double-blind treatment period (i.e. last trough observation carried forward) - The rate of incidence of oedema adverse events. 4 comparison groups: Telmisartan 80mg + Amlodipine 5mg,	Analysis of covariance	Fuall analysis set N=1057 Per protocol set N=950	Commercial/ Boehringer Ingelheim	Protocol, IPD, Data dictionary, CSR

	Telmisartan 40mg + Amlodipine 5mg, Amlodipine 10mg, Amlodipine 5mg	

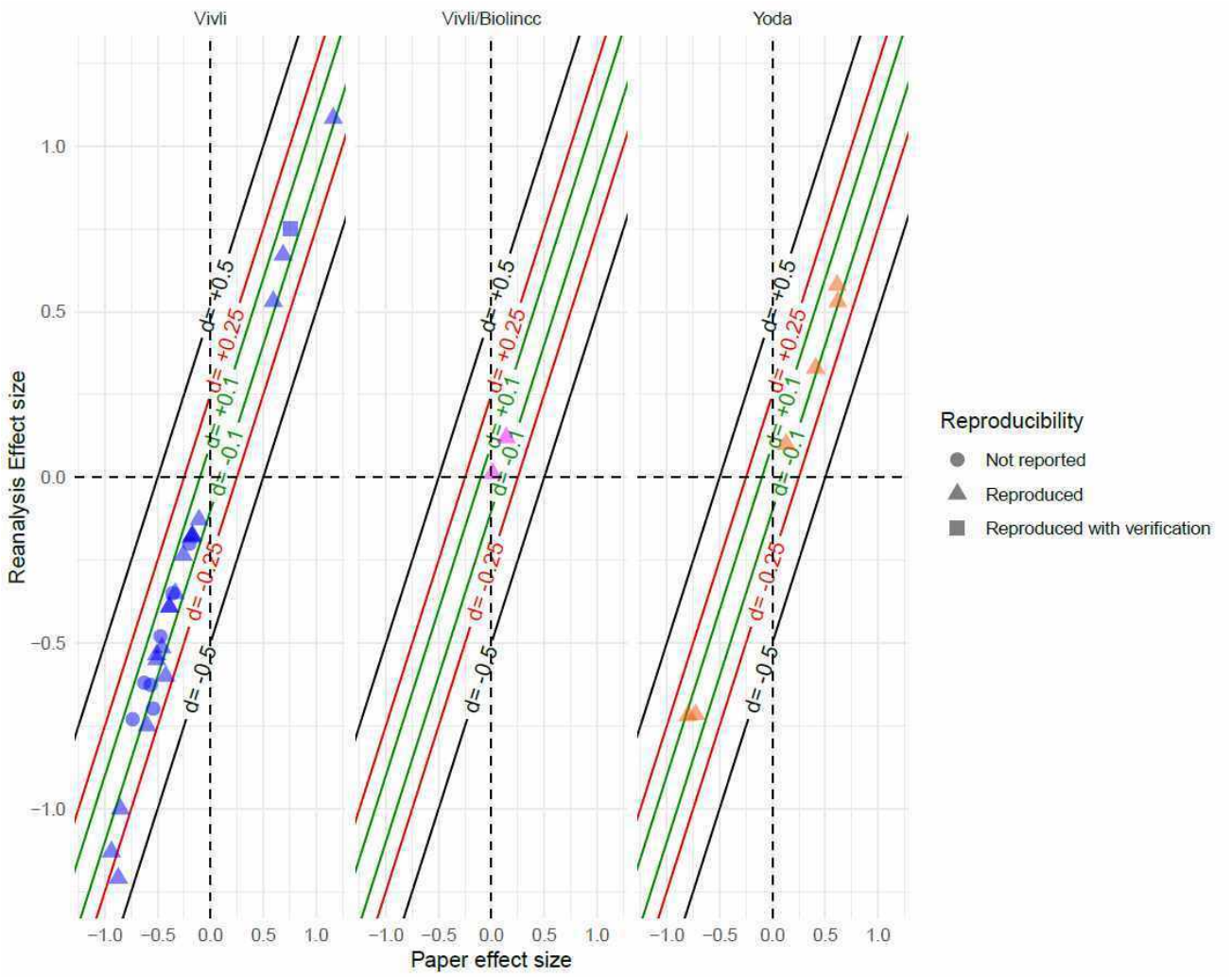


Figure 13: Original study effect size versus reanalysis effect size in publication (paper)

d: Cohen's d

The color of the bars represent the range of difference in point estimates between reanalysis and result in paper: green = ± 0.10, red = ± 0.25, black = ± 0.50

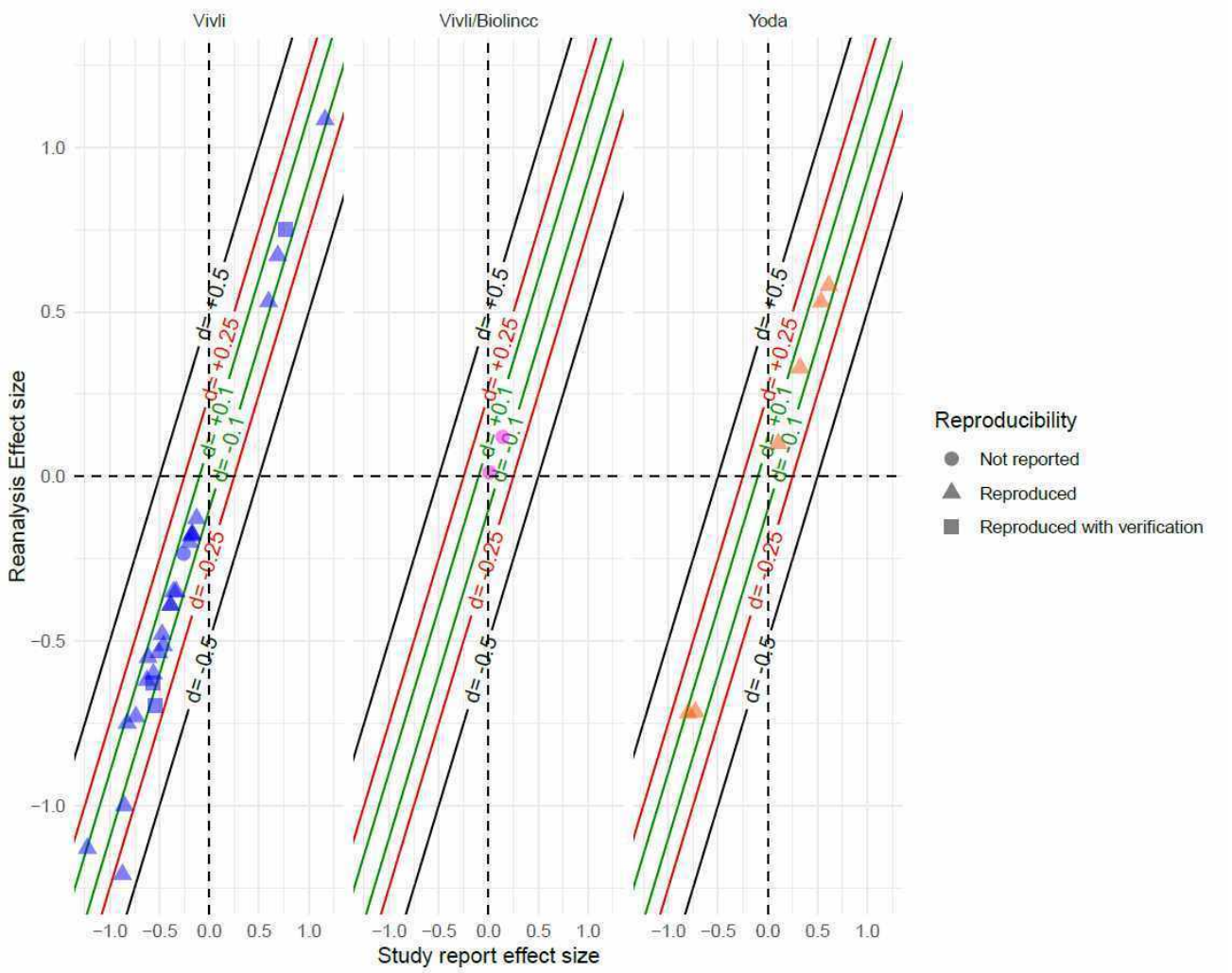


Figure 14: Original study effect size versus reanalysis effect size in study report

d: Cohen's d

The color of the bars represent the range of difference in point estimates between reanalysis and result in study report: green = ± 0.10, red = ± 0.25, black = ± 0.50

List of challenges

The main challenge during our study, was the long procedures of the registered report and the data request.

For the registered report, the entire peer review and acceptance process lasted from August 29 2019, 2020 to June 10, 2020, i.e. 9, 45 months. Because of the registered report format, we had to wait for in principle acceptance after this process before starting data collection by retrieving the RCTs available on data sharing platforms.

The data request process was time consuming too. The time between dates of the first contact and the access to the data was 11, 35 months for Vivli; 6, 35 months for YODA; 5, 67 months for BioLincc and 4, 35 months for Project Data Sphere.

The request process on Vivli takes a few months longer each time a new request is added to the initial data request. This happens when studies mainly identified on CSDR have their data transferred to Vivli and a new request must be made.

On CSDR, we had to wait for all the sponsors to respond before moving forward in the application process, which delayed the progress of the application process, because some sponsors took much longer than others to respond.

Prior to data access, a data sharing agreement had to be signed between both parties. The legal department of our unit had to verify and have the data agreement signed, which also took considerable time for certain reasons such as the Covid-19 pandemic which slowed down the administrative process of signing the document by our institution. The careful attention of our department regarding compliance with the GDPR significantly delayed the process.

As data access times have exceeded the 1 year set in our protocol and because these delays were partly caused by our institution, we have removed this condition from our protocol, in accordance with the editor.

Last, even after an accepted request, requesting additional data needed to reanalyse primary outcomes may delay a reanalysis, as sponsors may be slow to respond favourably. We are currently awaiting a response from a sponsor after requesting the data dictionary and statistical analysis plan for a study.

DISCUSSION

At this stage of our study, 18/21 (85.7%) reanalyses have inferentially reproduced the original results. When IPD and sufficient document are available, original results are generally inferentially reproduced. This conclusion was also made in another reproducibility project of the ReiTheR program submitted as a registered report. This second study involved a similar method to study the reproducibility of pivotal trials assessed by the European Public

Assessment Report (EPARs), for new authorized human medications and biosimilars approved by the European Medicines Agency (EMA). All the 23 distinct outcomes reanalysed were considered as inferentially reproduced (170). However, data were only obtained for ten of the 62 main trials for which data were requested. The reproducibility rate in this study was therefore 16%, due to the lack of IPD availability, despite the fact that a large majority of sponsors had a data-sharing policy. In our study, only 9,6% (6/62) data requests were denied to date.

This is in line with a scoping review by Ohmann *et al* which found that data access is rarely denied by platforms (37). It surely explains the higher percentage of data access through the sharing platform of data compared to other methods of requesting data. Moreover, this result suggests that studies shared on data sharing platforms may differ in meaningful ways from the population of trials not shared by the same entities.

Both those 2 Reither projects were submitted as a registered report and their twin protocol were peer-reviewed prior to data collection and analysis. Data availability was higher in the platform study and the scientific merit of the research question was not discussed unlike in the second registered report focused on. EMA approvals in which data access was often denied (in 9/62 cases) because of insufficient scientific merit.

We cannot exclude that the trials that are shared on data-sharing platforms are not a representative sample of all trials conducted to date. It is possible that are less prone to reproducibility issues. For example, studies on platforms may be subject to more stringent quality control with less risk of non-reproducibility.

To date, reanalyses of clinical trials are rarely performed, and even fewer by researchers independent of the original study team. In March 2014, Ebrahim *et al* identified a small number of reanalyses of RCTs and only a few were led by independent researchers. When assessing reproducibility, they found that 35% of published reanalyses led to changes in results that implied different conclusions than the original paper about the types and numbers of patients needed to be treated (171). This result is quite different from our result but it was based on a very selected sample of RCTs.

And in any case, such studies are always based on biased samples. In another cross-sectional study that aimed to explore the association between the ICMJE policy implementation and data availability and reproducibility of key findings among the top 10 surgical journals, had access to data for 2/65 trials published before and 2/65 published after the policy (172). Among the 65 studies published after the data sharing policy, 5 had a data sharing statement in their publication, with an intention to share data upon request. These data were not obtained because no correspondence could be established despite a strict application of the procedure detailed in the data sharing statement. All primary outcomes of the 4 RCTs with available study data were fully reproduced following the approach used by the initial authors.

Data sharing platforms surely helps in reducing barriers to access and reuse of data, by facilitating data sharing (173). However, challenges remain to increase transparency and sharing of clinical trial data to maximize data value. In a survey that investigated opinions and experiences of sharing of clinical trial data, 74% (236/683) of the responders thought that, in principle, sharing de-identified data through a data repository should be mandatory. Only 18%

(56/683) were required by their research funder to deposit their trial data in a repository, and 32 of the 56 (57%) had thus far deposited the data (174). Although data sharing is supported by many stakeholders, its practical implementation remains low, which calls into question the real impact of data sharing initiatives on the real improvement of the reproducibility and reliability of therapeutic research.

Limitations of the study

At this point in our study, we acknowledge some limitations. One limitation is the restriction of the re-analyses to primary endpoints. It would be interesting to evaluate secondary endpoints and safety endpoints, but we cannot guarantee that we will be able to re-analyze all the criteria used by the studies included, with the workload and the necessary resources that it would require (156). Another limitation is that we cannot exclude the possibility that an analysis may be classified as reproducible although inherently flawed as assessed by the re-analysis. But most importantly, as our study only includes clinical trials with data available on platforms, caution is advised before generalizing our results. Studies whose IPD is shared may differ in meaningful ways from those whose data is not shared. Last, this is of course a preliminary report and our results are definitive and may change.

Expected impact

Reports on RCTs are highly influential in the context of evidence-based medicine and there is currently a growing interest in sharing their results. In addition, patients support data-sharing (175). Therefore, the final results of this project are expected and we hope that they will have a high, direct impact on the medical community and patients/citizens. Since reproducibility is an important property in the scientific process, good inferential reproducibility (i.e. conclusions that remain after a new independent analysis) will probably be considered as an important characteristic of a well-conducted study. By studying data-sharing practices and their usefulness, we also hope that we will enhance the awareness of scientists, editors and funders towards these crucial, strategic issues and to advance the development of data-sharing policies and practices that maximize the use of best research practices.

The project will inform decision-makers of the usefulness and feasibility of large-scale data-sharing policies. It will also give indications to clinicians about the strength of the evidence they rely on to treat patients in their day-to-day practice. This study will in the future trigger efforts to produce good-practice guidelines for data-sharing.

Conclusion

Despite long delays, the main clinical data sharing platforms succeed in their ambition, which is to make access to data possible for external researchers, compared to other means of requesting data. Our preliminary results suggest that the re-analyses of clinical data shared by such platforms have good inferential reproducibility. Bearing in mind that it is likely that studies shared on data sharing platforms differs regarding several reproducibility features from the trials that are not shared by the same entities, these results provide fresh insights on reproducibility of therapeutic research.

CHAPITRE 5 : DISCUSSION

1- Quel est l'impact de l'adoption des politiques sur la disponibilité, le partage et la réutilisation des données issues d'essais cliniques ?

Aujourd'hui, les avantages de l'ouverture et du partage des données font consensus auprès des financeurs qui y voient une maximisation de l'utilisation des données et donc un meilleur retour sur investissement, un moyen d'accélérer l'amélioration de la santé publique et de faire une science de meilleure qualité (transparence, reproductibilité et fiabilité renforcées) lorsque les données sont mis à disposition des chercheurs de manière appropriée pour une utilisation secondaire (méta-analyse, confirmation et/ou vérification de résultats, formulation de nouvelles questions de recherche sur base de résultats existants) (176).

Dans la première partie de la thèse, la disponibilité des données issus d'essais clinique a été explorée en évaluant le pourcentage de financeurs, ayant mis en place une politique de partage de données. Les politiques recommandant ou exigeant le partage, avec des informations sur comment, où et quand avoir accès aux données, sont la première étape pour la promotion et l'application de l'ouverture des données (177).

Nous avons réalisé un état des lieux de l'adoption de politiques par les financeurs, afin d'évaluer l'engagement de ces derniers en faveur du partage de données, action clé de valorisation des données au-delà de l'objectif de l'étude originale pour l'innovation et l'avancement de la recherche scientifique (178).

Parmi un échantillon de 178 financeurs internationaux d'essais clinique, dont 100 financeurs commerciaux (compagnies pharmaceutiques) et 78 financeurs non commerciaux (institutions de recherche, fondations caritatives etc…), seuls 40% (71/178) avaient une politique de partage de données.

41 % des financeurs commerciaux (41/100) et 38 % (30/78) des financeurs non commerciaux avaient une politique de partage de données.

Parmi les financeurs non commerciaux ayant une politique de partage de données, 60% (18/30) font du partage de données issues d'études financées une obligation et 40% (12/30) recommandent le partage de données issues des études financées.

Sans surprise, notre sondage auprès des financeurs d'essais clinique en France montre que l'existence d'une politique de partage de données concerne uniquement que 19% du volume financier total (850032000 euros) des appels d'offres en recherche clinique de 2018 (26/31 financeurs inclus ont fournis l'information sur le volume financier de leurs appels d'offre). L'objectif de ce sondage était d'évaluer la mise en place des politiques de partage de données issus d'essais cliniques en France. Parmi les 31 financeurs dont nous avons récolté les réponses, 29% (9/31) avaient une politique de partage de données issus d'essais cliniques, dont 1/9 (11.1%) oblige au partage et 8/9 (88.8%) recommandent le partage de données. (179)

Nos résultats montrent que la proportion de financeurs d'essais cliniques ayant mis en place une politique est loin d'être optimale, ainsi que des taux insatisfaisants de mise œuvre de ces politiques de partage.

Pour évaluer la mise en œuvre des politiques de partage, nous avons vérifié la présence de déclarations de partage de données lors de l'enregistrement sur Clinicaltrials.gov d'un échantillon de 200 ECR (conformément aux recommandations de partage de données de l'ICMJE) ayant pour sponsor, les financeurs internationaux inclus dans notre échantillon d'analyse. L'intention de partage a été précisé pour seulement 12 % [7 % - 20 %] et 59 % [49 % - 69 %] des ECR financés par des financeurs non commerciaux et commerciaux, respectivement. 77% et 81% des enregistrements sur Clinicaltrials.gov comportaient des déclarations de partage pour les ECR financés par les financeurs non commerciaux et commerciaux, respectivement. (178)

Cette faible conformité aux politiques a été également retrouvée, lorsque nous nous sommes intéressés, dans le cadre d'une autre étude du projet Reither, aux politiques de partage des revues biomédicales, membres et affiliés de l'ICMJE. Seuls 57% (8/14) des revues membres de l'ICMJE et 30% (145/489) des journaux affiliés avaient une politique explicite de partage de données, et ne se réfèrent pas simplement aux exigences de l'ICMJE (180). Si le pourcentage de déclarations de partage de données est élevé pour les articles publiés par les journaux membres de l'ICMJE, ce n'est pas du tout le cas pour les articles publiés par les journaux affiliés où seuls 25% d'articles comportaient une déclaration et 22% une intention réelle de partage. (180)

Ce constat de manque de conformité aux recommandations d'ouverture et de partage de données perdure, même avec les études concernant le Covid-19. Une étude analysant les intentions de partage déclarées dans les enregistrements sur Clinicaltrials.gov et publications d'essais interventionnels sur le Covid-19, montre que seuls 15% des enregistrements comportaient une intention de partage et seuls 7 publications comportaient une déclaration de partage (181). Cette étude a été mis à jour, et les chiffres n'ont pas augmenté sur les intentions de partage précisés dans les enregistrements (182). Une autre étude, évaluant les déclarations de partage de 40 essais concernant 36 vaccins contre le Covid-19, a trouvé que seuls 31 avaient une déclaration de partage et seuls 25 donnaient un accès aux données sources (183).

Les indicateurs de disponibilité des données issus d'essais cliniques, étudiés lors des travaux de cette thèse relèvent, que les politiques de partage actuelles sont inefficaces pour garantir un partage effectif des données.

Bien que la disponibilité des données témoigne d'une transparence de l'étude, l'intérêt du partage de données réside dans leur réutilisation par des chercheurs extérieurs à l'équipe originale (184) (185). Un autre aspect de l'inefficacité des politiques des données actuelles est qu'elle ne garantit pas non plus une réutilisation des données. Une étude du projet Reither, montre que sur dix ans d'application de la politique de partage de la revue médicale Annals of Internal Medicine, les publications d'essais cliniques randomisés dans la revue ayant mentionné une volonté de partage de données, ne sont pas associées à une réutilisation importante des données partagées.(186)

Les performances des politiques actuelles de partage de données sont donc faibles pour faire évoluer les pratiques en matière de partage réelle et de réutilisation des données. **Comment s'assurer que les politiques de partage de données répondent à l'enjeu de la nécessaire amélioration des pratiques et de la reproductibilité en recherche clinique ?**

Nous avons exploré cette question dans un deuxième temps, en analysant les performances des recommandations de l'ICMJE.

Cette analyse s'appuie principalement sur les conclusions d'études du projet Reither. Celles-ci montrent que les recommandations de l'ICMJE sont telles quelles inadéquates et donc peu respectées. Nous suggérons alors que l'ICMJE devrait adopter une politique plus forte sur le partage de données, en incluant des méthodes d'évaluation pour s'assurer que les objectifs du partage soient atteints, le tout appuyé par des actions concertées et conjointes avec les chercheurs, les financeurs et les revues.(185)

Perspectives dans le rôle des financeurs

Les conclusions de la scoping review, réalisée par Ohman *et al*, dont l'objectif était d'explorer l'impact des initiatives du partage des données sur l'intention réel du partage des données et sur leur réutilisation montrent qu'il existe actuellement une absence de preuve sur l'impact potentiel des politiques de partage de données et sur l'impact de la pratique du partage de données issues d'essais cliniques. Ce manque d'informations entrainerait des incertitudes dans la mise en œuvre des recommandations de partage de données. (37)

Nous savons que le partage de données soulève des questions de confidentialité des données des patients, de coûts liés à l'anonymisation et à la préparation des données, de paternité de données qui empêcherait les chercheurs initiaux à partager car ils veulent exploiter et tirer profit au maximum des données durement acquises, de risque de mauvaise interprétation et de fusion inappropriée de jeux de données (187).

Les financeurs commerciaux, dont les politiques ne s'adressent pas à des chercheurs externes, ont des performances (en termes d'engagement au partage des données et de transparence) meilleures comparées à celles des financeurs non-commerciaux. Toutefois, ces politiques doivent être associées à une évaluation de leur impact afin de mesurer les progrès réellement réalisés. De plus que ces performances sont loin d'être optimales, l'amélioration des directives pour un réel partage des données est nécessaire. Comme Ohman *et al* le suggèrent, des « études interventionnelles devraient être exécuté pour déterminer la politique optimale de partage de données et / ou des incitations qui ajoutent de la valeur à la recherche clinique » [*interventional studies should be run to determine the optimal data-sharing policy and/or incentives that add value to clinical research*]

Concernant les financeurs de l'écosystème de la recherche académique, l'échec de leur politique de données pour faire du partage de données la norme, réside principalement dans la non assimilation des recommandations car elles sont perçues comme inadéquates aux besoins

des chercheurs, le manque de reconnaissance et de récompenses pour encourager les pratiques d'ouverture et de partage de données, et le manque de sanctions dans le cas de non-respect des politiques.

Les réticences par rapport à la nouvelle politique de partage de données de l'*US National Institutes of Health* NIH, qui rentrera en vigueur à partir du 25 Janvier 2023, relatent bien les défis que doivent relever les financeurs.

Avec la nouvelle politique du NIH, la mise à disposition des données scientifiques générées par les études financées par la NIH, dans des référentiels appropriés pour la préservation et le partage des données, **sera obligatoire** pour tous les bénéficiaires, sous peine de mettre en péril de futurs financements (188).

Les chercheurs trouvent déjà des obstacles à la réussite des objectifs cette nouvelle politique (189).

La politique du NIH fait mention de « données scientifiques » et laisse les chercheurs dans l'imprécision du type de données à partager. Même s'il a été suggéré lors des révisions de la politique que les exigences de la NIH se limitent uniquement aux données reliées à des publications, l'agence américaine, par la voix de sa directrice par intérim Jorgenson, a précisé que les données à partager concernent les données collectées qui sont dans les publications, et ceux qui ne le sont pas car ces dernières sont tout autant importantes pour aider d'autres chercheurs à comprendre l'expérience menée. Ce manque de précisions de la nouvelle politique NIH sur les données à conserver pour un futur partage est pointé par des chercheurs dans un article de Nature, et remet à jour la complexité de la définition d'une donnée de recherche et le choix des données qui valent la peine d'être conservées ou pas (et donc mis à disposition pour un partage). (189)

Quelles données valent la peine d'être conservées pour le partage ?

De cette question, découle également les préoccupations liées aux coûts des ressources que peuvent nécessiter la préparation des données au partage.

Les chercheur(e)s craignent le travail supplémentaire et les ressources que nécessiterait le traitement de données à partager qu'exige la nouvelle politique du NIH même si certains frais liés à la gestion des données sont pris en charge. Naudet *et al*, relatent que certains auteurs leur ont demandé de couvrir des frais de préparation des données comme condition de partage, ce qui a conduit à une impossibilité de réanalyser ces études sans moyens spécifiquement dédiées (101).

La bonne gestion des données est certes une bonne pratique, mais a besoin d'être accompagnée par des ressources financières et de compétences techniques. Ces derniers doivent être considérées par les financeurs pour améliorer l'adhérence à l'ouverture et au partage de données. Les solutions de stockage, de partage et d'harmonisation des données sont des exemples de préoccupations des chercheurs.

Christine L. Borgman, conclut dans son livre *Qu'est-ce que le travail scientifique des données ? Big data, little data, no data* qu'il n'y a pas de « réponse toute faite à la question « quelles

données garder ? », parce qu'il n'y a pas non plus de réponse toute faite à la question « qu'est-ce qu'une donnée ? » » (68). Pour cette chercheuse, trouver des nouveaux usages aux données peut maximiser leur valeur mais cela relève du spéculatif car « prévoir parfaitement les futurs usages » ne peut être vrai pour toutes les données issues d'une recherche ; certaines données ont alors une valeur éphémère. Borgman décrète qu'il est alors important d'arriver à un consensus entre les parties prenantes sur le type de donnée à garder, donc à partager et y investir les ressources nécessaires qui « ne peuvent reposer sur les seules épaules des chercheurs et chercheuses ».

Pasquetto, dans sa thèse sous la direction de Borgman, s'est intéressé aux défis sociotechniques, épistémiques et éthiques liées à l'ouverture et à la réutilisation des données de la recherche biomédicale, en étudiant un consortium américain pour le partage de données DataFace. Ses travaux montrent que les chercheur(e)s biomédicaux ne téléchargent, ni ne réanalysent les données de recherche non reliées à une publication, c'est-à-dire des ressources sans hypothèses (190).

Il serait alors tentant de dire que le partage de données ne devrait concerner que les données reliées à une publication et que les financeurs devraient soutenir et mettre en place des solutions de conservation à long terme de ces données, car potentiellement réutilisables et à potentiel innovateur des soins médicaux et d'autres questions relatives à la santé publique. Ce serait alors oublier la littérature grise, concernant le nombre important de résultats non publiés d'études pour diverses raisons (résultats négatifs, petite taille de l'effet, manque de temps des chercheurs). Les biais de déclaration « *reporting bias* » liés à la publication sélective des résultats, ou à l'absence de publication de résultats, sont bien connus comme problème majeur affectant la validité des preuves dans tous les domaines de la recherche biomédicale (6).

Les avantages du partage de données ne seraient pleinement obtenus que si chaque étude financée, ayant ainsi produit des données soit transparente, découvrable en ayant une trace dans la littérature, pour une réutilisation. La transparence des données et le partage de données sont deux principes distincts, qui ne peuvent contribuer à l'amélioration de la recherche seuls, la transparence étant un prérequis du partage de données.

Il est alors important que les financeurs commerciaux comme non commerciaux soutiennent les initiatives de méta-recherche qui démontrent l'utilité des principes de transparence et de partage dans la pratique médicale, ceci pour une meilleure adhésion au partage des données. Un exemple est l'initiative RIAT *Restoring Invisible and Abandonned Trials*, menée par Peter Doshi et ses collègues, dont le but est de tacler les biais de déclaration et améliorer la transparence de la recherche clinique en publiant les résultats d'essais « abandonnés ». Grâce au partage de données, et à l'accès de documents comme les rapports d'études ou les pré-enregistrements, des essais dont les résultats n'étaient pas publiés, ou avec des distorsions dans les résultats publiés, peuvent être réanalysés, pour une meilleure fiabilité des preuves sur lesquelles se basent les décisions de soins.

Les nouvelles exigences du NIH sont pressenties comme celles qui donnerait le *la* aux autres agences de financement pour adopter une politique similaire, qui semble aller au-delà du principe « aussi ouvert que possible aussi fermé que nécessaire ». Aussi, les Plan de gestion de

données demandés seront évalués et approuvés par l'institut avant l'attribution du financement. L'évaluation des plans de gestion par les agences de financement est jusque-là peu, ou pas du tout réalisée, or les politiques de partage de données sont principalement basées sur la demande de ce document, pour inciter les chercheurs à penser dès le début de leur recherche, à préparer leurs données pour un partage éventuel. La rédaction de ce document est alors considérée par certains chercheurs comme une charge administrative. Valoriser le plan de gestion de données, en vérifiant la conformité de ce que le chercheur y a décrit avec sa méthodologie réelle, serait un garde-fou pour préserver la qualité de la science et s'assurer d'un impact réel des politiques de données sur la pratique. De cette évaluation pourra découler les incitations pour récompenser les chercheurs avec des pratiques de transparence et de partage des données, ou des sanctions pour les chercheurs reluctants à ces pratiques.

Cette nouvelle politique du NIH plus exigeante est un espoir dans l'évolution des politiques de partage de données, pour faire changer la pratique, mais à condition de prendre en compte les motivations scientifiques du partage qui concernent l'évaluation la reconnaissance des chercheurs.

L'une d'entre elles est la valeur que donne les chercheurs à leurs données, qui répond à mon avis, au manque de respect des politiques de partage, initiées par les financeurs ou les revues. Violaine Rebouillat, dans sa thèse, a étudié « quelles formes de gestion et de partage existent dans les communautés de recherche et par quoi sont-elles motivées » en réalisant une enquête auprès de 57 chercheurs de l'Université de Strasbourg (191). Elle montre que les données ont une valeur d'usage (sert à publier des articles par exemple) et une valeur d'échange (dans le cadre d'une collaboration) à celui qui les a générés. Dans les deux cas, l'intérêt pour le chercheur est d'en tirer une certaine reconnaissance professionnelle : reconnaissance de ses pairs, perspectives de financement, futures collaborations. Ainsi, le partage de données répond à un besoin spécifique car il s'intègre dans « la stratégie du chercheur, de son équipe de recherche ou de sa communauté ». Pour encourager les bonnes pratiques et faire du partage de données une réalité, il faut que les politiques de partage s'alignent dans cette logique de valeur.

Selon Sarah Jones, dans son article « *Developments in Research Funder Data Policy* », le partage des données se produit de manière plus cohérente dans les cas où la communauté voit un avantage scientifique…la pratique de la gestion et du partage des données dépend de la volonté et de l'intérêt personnel de chacun, donc pour mettre les politiques en pratique, nous devons persuader [*Data sharing occurs most coherently in cases wherethe community sees scientific benefit or simply has to share to undertake research,such as in molecular biology…Data management and sharing practice is down to individual will and self-interest, so to turn policies into practice we need to persuade people*]. Elle ajoute : « La reconnaissance en termes d'évaluation de la recherche et de développement de carrière serait de puissants facteurs de motivation » [Recognition *in terms of research assessment and career development would be powerful motivators*.].

En mettant en place des recommandations claires et adaptées à la pratique scientifique, les financeurs pourraient mettre en place un environnement propice à l'ouverture et au partage des données. Cela n'est pas une tâche qui revient aux financeurs uniquement, mais à toutes les

parties prenantes qui doivent ensemble, relever le défi de « rendre les données découvrables, utilisables, évaluables, intelligibles et interprétables, le tout pour de longues périodes » (68).

Le monde de la recherche est en pleine transformation avec la volonté de faire du partage de données une réalité et des efforts en ce sens sont déployés.

La réforme de l'évaluation de la recherche est en marche avec des initiatives comme la Déclaration de San Francisco, signé par plusieurs parties prenantes et récemment l'Appel de Paris (192), un texte présenté par le Comité de la science ouverte à l'occasion des Journées Européennes de la science ouverte qui appelle les agences de financement, les institutions de recherche et les autorités d'évaluation et autres à s'engager pour une réforme du système actuel d'évaluation de la recherche. Valoriser la diversité des activités et des productions de recherches y compris les données, récompenser la conduite appropriée de la recherche, les bonnes pratiques comme le partage des résultats et des méthodologies de recherche font partie des engagements des signataires de l'appel de Paris. L'appel de Paris se concrétise avec une publication d'un accord sur la réforme de l'évaluation de la recherche, qui pourra être signé par tout organisme à but lucratif, impliqué dans l'évaluation de la recherche, afin de s'engager à réfléchir et à travailler ensemble pour réaliser la réforme par le biais d'une coalition d'organismes de financement de la recherche, de sociétés savantes, d'organisations de recherche. Un des moyens envisagés pour aider à la mise en œuvre de cet accord, est l'utilisation d'un CV narratif des chercheurs, qui permettra de mettre en valeur les études réalisées à l'aide de données partagées, ou sur des collaborations. « La révolution des données ouvertes ne se produira que si le système de recherche accorde autant d'importance au partage des données qu'à la paternité des articles. » [*The open data revolution won't happen unless the research system values the sharing of data as much as authorship on papers.*](193)

L'initiative des ateliers de la donnée en France, dans le cadre du Plan National de la Science Ouverte (PNSO) est un exemple d'appui en compétence soutenu par les financeurs. La mise en place de ces ateliers de la données a pour objectif de conseiller, d'accompagner les équipes de recherche afin de ne pas les laisser seules face aux défis du traitement de données (194). Cette initiative pourrait être discipline-centrée sur la recherche clinique. Toujours dans le cadre du PNSO, un projet soutenu par le fonds national pour la science ouverte, vise à rédiger une déclaration de partage de données d'essai clinique, qui sera à terme mis à disposition des chercheurs pour les aider à un partage de données avec suffisamment d'informations et de garanties sur la protection des données des patients.

2- Exploration de la reproductibilité de la recherche thérapeutique

L'accès aux données d'un échantillon aléatoire de 62 essais contrôlés et randomisés, de Phase 3, sans distinction en termes de design, de comparateur ou de patients a été demandé via quatre plateformes des plus importants en recherche clinique : Yoda, CSDR, VIVLI et Project Data Sphere.

Nous avons utilisé des méthodes de recherche reproductibles, en enregistrant les protocoles sur Open Science Framework, et en utilisant le format de publication « Registered report », format selon lequel le protocole d'étude a été évalué par les pairs et l'article final accepté de principe pour publication, avant toute collecte de données.

L'étude étant toujours en cours, les résultats présentés dans ce manuscrit sont préliminaires. Ils portent sur 21 essais dont les données ont été obtenues et réanalysées. Les résultats finaux seront présentés dans un article accepté de principe pour publication dans la revue Royal Society Open Science.

Les résultats préliminaires suggèrent un pourcentage d'accessibilité élevé des données d'essais cliniques via les plateformes de partage et une reproductibilité inférentielle plutôt bonne.

A ce jour, 6/62 demandes ont été refusés. En parallèle, nous avons conclus à la reproductibilité inférentielle de 18 sur 21 (85.7%) essais réanalysés. A la vue de ces chiffres, il est fort probable que nos résultats finaux rapportent un pourcentage de reproductibilité élevé.

Une seconde étude de reproductibilité du projet ReiTher, a conclu à une reproductibilité inférentielle de 16.1% sur un échantillon de 62 essais cliniques fournis à l'EMA dans le cadre d'une autorisation de mise sur le marché (170). Ce faible pourcentage de reproductibilité est expliqué par le faible nombre de données rendues accessibles : sur les 62 demandes de données, seules 10 ont été acceptées. Néanmoins, toutes les données obtenues ont été réanalysées avec succès.

En comparant les deux études ReiTher, nous constatons que les études sont largement reproduites lorsque les données sont accessibles. Ce qui confirme l'idée que les changements dans les conclusions suite à une nouvelle analyse ne sont pas si fréquents (101). De précédentes réanalyses ont également largement reproduits les résultats originaux quand les chercheurs partagent leurs données (101) (172).

Nous discuterons des difficultés rencontrées pendant l'analyse des données s'il y en a, dans notre rapport final. A ce stade, nous n'avons soulevé aucun doute sur la méthodologie initiale des essais réanalysés.

Toutefois, nous ne pouvons exclure l'hypothèse que les essais cliniques disponibles sur les plateformes de partage, ou en général, les essais dont les données sont partagées, diffèrent d'essais non disponibles. Les essais disponibles sur les plateformes peuvent être soumis à un contrôle qualité plus strict, et donc moins de risque de non-reproductibilité. Après tout, la décision de rendre accessible les données d'un essai est à la volonté du sponsor. Celle-ci doit dépendre surement de la valeur des données, qui peut représenter un enjeu financier considérable pour les sponsors d'essais cliniques. Le risque de mauvaise presse que peut entrainer des doutes sur la reproductibilité d'une étude étant l'un des arguments en défaveur du partage de donnée.

Les financeurs (notamment les financeurs commerciaux), ont activement contribué à la création de plateformes de partage de données d'essais cliniques, par lesquels les chercheurs peuvent demander, partager et avoir accès à des données dé-identifiées et anonymisées, pour des utilisations secondaires. L'accès aux données étant facilité, les avantages du partage peuvent

être obtenus, tout en minimisant les risques associés. Les essais peuvent être reproduits, afin d'améliorer la conception de futures recherches, pour la génération de nouvelles connaissances. Cependant, des défis subsistent pour accroître la transparence et le partage des données des essais cliniques afin de maximiser la valeur des données. Le faible partage de données durant la crise sanitaire de Covid-19 en est un exemple. Naomi Waithira, responsable de la gestion des données à l'Unité de recherche MORU Mahidol Oxford Research Unit, remarque que le partage des données pendant cette période était inférieur aux attentes. « Lorsque les demandes sont suivies, les chiffres sont nettement inférieurs, même lorsque les chercheurs demandent des données dont le partage avait été promis », affirme-t-elle lors d'une session de travail de la Covid-19 Clinical Researh Coalition. (195)

De rapides progrès scientifiques exigent de la transparence, et de cette dernière, dépend la reproductibilité. Comme le souligne Gundersen, la reproductibilité est un cas spécifique de réutilisation qui dépend de la disponibilité des données et documents nécessaires à une nouvelle exécution de l'étude. (25)

La reproductibilité peut être explorée de plusieurs manières. Ici, l'objectif de notre réanalyse est de retrouver des résultats et des conclusions qualitativement similaires, en utilisant les méthodes décrites dans le protocole pour conclure à une reproductibilité inférentielle. Cependant, cette méthode ne peut exclure la possibilité de parfaitement reproduire une étude dont les méthodes sont discutables. Une étude (172) portant sur la réanalyse d'essais publiés dans les dix principales revues chirurgicales, soulèvent cette limite dans la vérification de résultats principaux, en suivant les méthodes des chercheurs initiaux. Par exemple, pour une étude (196), les auteurs ont conclu à une reproductibilité des résultats de l'étude concernée, en utilisant la méthode des auteurs qui n'imputaient pas les valeurs manquantes. Néanmoins, dans cette étude « négative », une gestion différente et optimale des valeurs manquantes (autour de 50%) aurait pu conduire à des estimations différentes en termes de taille d'effet . Plus inquiétant, le nombre de données manquantes n'étaient pas indiqué dans l'article original.

Borgman relève que « les essais cliniques de médicaments et de procédures médicales sont préoccupés par la réplication et la vérification ». Elle distingue également deux types d'avis sur les tentatives de reproductions d'études en recherche clinique : ceux qui estime que les études de reproductibilité permettent « d'éviter des investissements erratiques », et ceux qui « pensent que la situation révèle les failles de la méthode scientifique ». (68)

Toutefois, certains chercheurs appellent à ne pas se focaliser sur la réplication comme unique moyen de validation de résultats.

Anne Scheel, dans son article *Why most psychological research findings are not even wrong*, affirme que la crise de la reproductibilité ne peut être résolue uniquement avec une rigueur dans la collecte et l'analyse des données. Les chercheurs devraient d'abord s'assurer de la bonne formulation des hypothèses, qui, selon elle, sont trop vagues. Essayer de reproduire des hypothèses mal formulées ne servirait pas à l'avancée des connaissances (197). Bien que cela n'était pas l'objet de notre recherche, c'est une remarque que nous nous sommes aussi faites dans le cadre de nos réanalyses. Les questions formulées (en termes de population, comparateur

et de critère de jugement) ne nous semblaient pas toujours optimales pour répondre à une question cliniquement pertinente.

Penders et Janssens, affirmaient qu'une étude non reproduite n'est pas nécessairement de qualité inférieure et peut offrir des opportunités d'apprendre, d'améliorer la recherche (54). Reproduire des études de façon indépendante ne suffirait pas à renforcer la validité de la recherche. En utilisant une même approche méthodologique, les résultats de la réplication d'une étude fausse seront systématiquement biaisés ou incorrects. C'est ce que défend certains chercheurs comme Munafò (un des auteurs du manifeste pour la reproductibilité), qui appellent à la triangulation des preuves (198). La triangulation est définie comme une utilisation stratégique d'approches multiples pour répondre à une question. Plus précisément, elle consiste à obtenir des réponses plus fiables aux questions de recherche, en intégrant les résultats de plusieurs approches différentes d'autres chercheurs. Les principales sources de biais pour chaque approche étant explicitement identifiées, elle permet un meilleur contrôle des biais. (199) (200)

Cette approche valorise la collaboration multidisciplinaire entre équipes scientifiques et vise à améliorer la transparence et la robustesse de la recherche scientifique. Cependant, elle est peu pratiquée et l'environnement scientifique reste concurrentiel (198). La duplication des essais sur le Covid-19, qui aurait pu être organisées d'une manière à en tirer des conclusions de plus grande puissance statistique en est un exemple.

La crise pourrait changer de camp, devenir une crise d'hypothèses, ou une crise de tout manquement de la pratique scientifique. Pour cela, des moyens doivent être mobilisés, pour soutenir et défendre les actions accompagnées d'un système d'évaluation d'impact, visant à faire avancer la culture d'une science transparente.

CONCLUSION GENERALE

Les politiques de partage de données sont des leviers importants pour l'amélioration de la reproductibilité de la recherche thérapeutique.

Dans un contexte de crise de reproductibilité, l'adoption des politiques par les financeurs, démontrent leur engagement à soutenir une recherche transparente et l'accès facile aux données de recherche financées.

Les résultats des travaux de cette thèse suggèrent que les politiques actuelles des financeurs manquent d'efficacité pour répondre à l'urgence d'amélioration des pratiques et de la reproductibilité en recherche clinique.

L'utilisation des outils tels que les plateformes facilitent l'accès aux données. L'utilisation de tels outils et l'application de pratiques de méta-recherche doivent être soutenues pour renforcer la validité des conclusions des essais.

Pour asseoir une réelle culture du partage de données issues d'essais cliniques, le défi des financeurs est d'accompagner leurs politiques de composantes d'évaluation, en consacrant des ressources nécessaires pour le respect des exigences. Aussi, faut-il que ces actions soient établies de manière en concertée avec les autres acteurs de la recherche, afin de transformer les intentions de bonnes pratiques en réelles applications.

REFERENCES

1. Fecher B, Friesike S. Open Science: One Term, Five Schools of Thought. In: Bartling S, Friesike S, éditeurs. Opening Science: The Evolving Guide on How the Internet is Changing Research, Collaboration and Scholarly Publishing [Internet]. Cham: Springer International Publishing; 2014 [cité 8 avr 2022]. p. 17-47. Disponible sur: https://doi.org/10.1007/978-3-319-00026-8_2

2. Yozwiak NL, Schaffner SF, Sabeti PC. Data sharing: Make outbreak research open access. Nature. févr 2015;518(7540):477-9.

3. Besançon L, Peiffer-Smadja N, Segalas C, Jiang H, Masuzzo P, Smout C, et al. Open science saves lives: lessons from the COVID-19 pandemic. BMC Med Res Methodol. 5 juin 2021;21(1):117.

4. Kiley R, Peatfield T, Hansen J, Reddington F. Data Sharing from Clinical Trials — A Research Funder's Perspective. N Engl J Med. 16 nov 2017;377(20):1990-2.

5. Navar AM, Pencina MJ, Rymer JA, Louzao DM, Peterson ED. Use of Open Access Platforms for Clinical Trial Data. JAMA. 22 mars 2016;315(12):1283-4.

6. Munafò MR, Nosek BA, Bishop DVM, Button KS, Chambers CD, Percie du Sert N, et al. A manifesto for reproducible science. Nat Hum Behav. 10 janv 2017;1(1):1-9.

7. Le Plan national pour la science ouverte : les résultats de la recherche scientifique ouverts à tous, sans entrave, sans délai, sans paiement [Internet]. enseignementsup-recherche.gouv.fr. [cité 12 mai 2022]. Disponible sur: https://www.enseignementsup-recherche.gouv.fr/fr/le-plan-national-pour-la-science-ouverte-les-resultats-de-la-recherche-scientifique-ouverts-tous-49241

8. Bartling S, Friesike S. Towards Another Scientific Revolution. In: Bartling S, Friesike S, éditeurs. Opening Science: The Evolving Guide on How the Internet is Changing Research, Collaboration and Scholarly Publishing [Internet]. Cham: Springer International Publishing; 2014 [cité 7 avr 2022]. p. 3-15. Disponible sur: https://doi.org/10.1007/978-3-319-00026-8_1

9. David PA. The Historical Origins of « Open Science »: An Essay on Patronage, Reputation and Common Agency Contracting in the Scientific Revolution [Internet]. Rochester, NY: Social Science Research Network; 2013 janv [cité 7 avr 2022]. Report No.: 2209188. Disponible sur: https://papers.ssrn.com/abstract=2209188

10. Moore SA. A genealogy of open access: negotiations between openness and access to research. Rev Fr Sci L'information Commun [Internet]. 1 août 2017 [cité 8 avr 2022];(11). Disponible sur: https://journals.openedition.org/rfsic/3220

11. Cohen É, Goetschel P. L'Open Access vu par deux historiennes. Soc Represent. 2 juill 2014;37(1):143-54.

12. Libre accès à l'information scientifique et technique - Textes de références - Déclaration de Berlin sur le Libre Accès à la Connaissance en sciences exactes, sciences de la vie, sciences humaines et sociales [Internet]. [cité 8 avr 2022]. Disponible sur: https://openaccess.inist.fr/declaration-de-berlin-sur-le-libre-acces-a-la-connaissance-en-sciences-exactes-sciences-de-la-vie-sciences-humaines-et-sociales/

13. Klump J, Bertelmann R, Brase J, Diepenbroek M, Grobe H, Höck H, et al. Data publication in the open access initiative. Data Sci J. 2006;5:79-83.

14. Déclaration de Berlin sur le Libre Accès à la Connaissance en Sciences exactes, Sciences de la vie, Sciences humaines et sociales [Internet]. [cité 15 mai 2022]. Disponible sur: https://www.ouvrirlascience.fr/declaration-de-berlin-sur-le-libre-acces-a-la-connaissance-en-sciences-exactes-sciences-de-la-vie-sciences-humaines-et-sociales

15. Ramachandran R, Bugbee K, Murphy K. From Open Data to Open Science. Earth Space Sci. 2021;8(5):e2020EA001562.

16. Pontika N, Knoth P, Cancellieri M, Pearce S. Fostering open science to research using a taxonomy and an eLearning portal. In: Proceedings of the 15th International Conference on Knowledge Technologies and Data-driven Business [Internet]. New York, NY, USA: Association for Computing Machinery; 2015 [cité 11 avr 2022]. p. 1-8. (i-KNOW '15). Disponible sur: https://doi.org/10.1145/2809563.2809571

17. Plesser HE. Reproducibility vs. Replicability: A Brief History of a Confused Terminology. Front Neuroinformatics. 18 janv 2018;11:76.

18. Claerbout JF, Karrenbach M. Electronic documents give reproducible research a new meaning. In: SEG Technical Program Expanded Abstracts 1992 [Internet]. Society of Exploration Geophysicists; 1992 [cité 13 avr 2022]. p. 601-4. (SEG Technical Program Expanded Abstracts). Disponible sur: https://library.seg.org/doi/abs/10.1190/1.1822162

19. Rougier NP, Hinsen K, Alexandre F, Arildsen T, Barba L, Benureau FCY, et al. Sustainable computational science: the ReScience initiative. PeerJ Comput Sci. 18 déc 2017;3:e142.

20. Peng RD, Dominici F, Zeger SL. Reproducible Epidemiologic Research. Am J Epidemiol. 1 mai 2006;163(9):783-9.

21. Currie LA, Svehla G. Nomenclature for the presentation of results of chemical analysis (IUPAC Recommendations 1994). Pure Appl Chem. 1 janv 1994;66(3):595-608.

22. JCGM - Joint Committee for Guides in Metrology [Internet]. [cité 13 avr 2022]. Disponible sur: https://www.iso.org/sites/JCGM/VIM-JCGM200.htm

23. Artifact Review and Badging – Version 1.0 (not current) [Internet]. [cité 13 avr 2022]. Disponible sur: https://www.acm.org/publications/policies/artifact-review-badging

24. Goodman SN, Fanelli D, Ioannidis JPA. What does research reproducibility mean? Sci Transl Med. juin 2016;8(341):341ps12-341ps12.

25. Gundersen OE. The fundamental principles of reproducibility. Philos Trans R Soc Math Phys Eng Sci. 17 mai 2021;379(2197):20200210.

26. Directorate-General for Research and Innovation (European Commission), Baker L, Cristea IA, Errington TM, Jaśko K, Lusoli W, et al. Reproducibility of scientific results in the EU: scoping report [Internet]. LU: Publications Office of the European Union; 2020 [cité 17 mai 2022]. Disponible sur: https://data.europa.eu/doi/10.2777/341654

27. Chen X, Dallmeier-Tiessen S, Dasler R, Feger S, Fokianos P, Gonzalez JB, et al. Open is not enough. Nat Phys. févr 2019;15(2):113-9.

28. Stark PB. Before reproducibility must come preproducibility. Nature. 24 mai 2018;557(7707):613-613.

29. Lyon L. Transparency: the emerging third dimension of Open Science and Open Data. Liber Q J Assoc Eur Res Libr. 23 juin 2016;25(4):153-71.

30. Resnik DB, Elliott KC. Value-entanglement and the integrity of scientific research. Stud Hist Philos Sci Part A. 1 juin 2019;75:1-11.

31. Décret n° 2021-1572 du 3 décembre 2021 relatif au respect des exigences de l'intégrité scientifique par les établissements publics contribuant au service public de la recherche et les fondations reconnues d'utilité publique ayant pour activité principale la recherche publique - Légifrance [Internet]. [cité 11 juill 2022]. Disponible sur: https://www.legifrance.gouv.fr/jorf/id/JORFTEXT000044411360

32. Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. Retraction: Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19. N Engl J Med. DOI: 10.1056/NEJMoa2007621. N Engl J Med. 25 juin 2020;382(26):2582-2582.

33. Mehra MR, Desai SS, Ruschitzka F, Patel AN. RETRACTED: Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. The Lancet [Internet]. 22 mai 2020 [cité 25 mai 2022];0(0). Disponible sur: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31180-6/fulltext#seccestitle160

34. Davey M, Kirchgaessner S, Boseley S. Surgisphere: governments and WHO changed Covid-19 policy based on suspect data from tiny US company. The Guardian [Internet]. 3 juin 2020 [cité 23 août 2022]; Disponible sur: https://www.theguardian.com/world/2020/jun/03/covid-19-surgisphere-who-world-health-organization-hydroxychloroquine

35. A mysterious company's coronavirus papers in top medical journals may be unraveling [Internet]. [cité 23 août 2022]. Disponible sur: https://www.science.org/content/article/mysterious-company-s-coronavirus-papers-top-medical-journals-may-be-unraveling

36. Begley CG, Ioannidis JPA. Reproducibility in Science. Circ Res. 2 janv 2015;116(1):116-26.

37. Ohmann C, Moher D, Siebert M, Motschall E, Naudet F. Status, use and impact of sharing individual participant data from clinical trials: a scoping review. BMJ Open. 18 août 2021;11(8):e049228.

38. Earning the public's trust. Sci Adv. 9 mars 2022;8(10):eabo6347.

39. Ioannidis JPA. Why Most Published Research Findings Are False. PLOS Med. 30 août 2005;2(8):e124.

40. Ioannidis JPA, Stanley TD, Doucouliagos H. The Power of Bias in Economics Research. Econ J. 2017;127(605):F236-65.

41. Stagge JH, Rosenberg DE, Abdallah AM, Akbar H, Attallah NA, James R. Assessing data availability and research reproducibility in hydrology and water resources. Sci Data. 26 févr 2019;6(1):190030.

42. Baker M. 1,500 scientists lift the lid on reproducibility. Nature. 1 mai 2016;533(7604):452-4.

43. Begley CG, Ellis LM. Raise standards for preclinical cancer research. Nature. mars 2012;483(7391):531-3.

44. OPEN SCIENCE COLLABORATION. Estimating the reproducibility of psychological science. Science. 28 août 2015;349(6251):aac4716.

45. Errington TM, Denis A, Perfito N, Iorns E, Nosek BA. Challenges for assessing replicability in preclinical cancer biology. Rodgers P, Franco E, éditeurs. eLife. 7 déc 2021;10:e67995.

46. Loscalzo J. Experimental Irreproducibility: Causes, (Mis)interpretations, and Consequences. Circulation. 13 mars 2012;125(10):1211-4.

47. Hensel PG. Reproducibility and replicability crisis: How management compares to psychology and economics – A systematic review of literature. Eur Manag J. 1 oct 2021;39(5):577-94.

48. Stroebe W, Postmes T, Spears R. Scientific Misconduct and the Myth of Self-Correction in Science. Perspect Psychol Sci. 1 nov 2012;7(6):670-88.

49. Drimer-Batca D, Iaccarino JM, Fine A. Status of retraction notices for biomedical publications associated with research misconduct. Res Ethics. 1 avr 2019;15(2):1-5.

50. Fanelli D. Is science really facing a reproducibility crisis, and do we need it to? Proc Natl Acad Sci. 13 mars 2018;115(11):2628-31.

51. Fanelli D. Why Growing Retractions Are (Mostly) a Good Sign. PLOS Med. 3 déc 2013;10(12):e1001563.

52. Jamieson KH. Crisis or self-correction: Rethinking media narratives about the well-being of science. Proc Natl Acad Sci U S A. 13 mars 2018;115(11):2620-7.

53. Oreskes N. Beware: transparency rule is a Trojan Horse. Nature. 1 mai 2018;557(7706):469-70.

54. Penders B, Janssens ACJW. Finding Wealth in Waste: Irreplicability Re-Examined. BioEssays. 2018;40(12):1800173.

55. Amrhein V, Greenland S, McShane B. Scientists rise up against statistical significance. Nature. mars 2019;567(7748):305-7.

56. Earp BD, Trafimow D. Replication, falsification, and the crisis of confidence in social psychology. Front Psychol [Internet]. 2015 [cité 10 mai 2022];6. Disponible sur: https://www.frontiersin.org/article/10.3389/fpsyg.2015.00621

57. Schmidt S. Shall we really do it again? The powerful concept of replication is neglected in the social sciences. Washington, DC, US: American Psychological Association; 2016. 581 p. (Methodological issues and strategies in clinical research, 4th ed).

58. Braude SE. ESP and Psychokinesis: A Philosophical Examination. Universal-Publishers; 2002. 247 p.

59. Peterson D, Panofsky A. Metascience as a scientific social movement [Internet]. SocArXiv; 2020 [cité 24 mai 2022]. Disponible sur: https://osf.io/preprints/socarxiv/4dsqa/

60. Nosek BA, Bar-Anan Y. Scientific Utopia: I. Opening Scientific Communication. Psychol Inq. 1 juill 2012;23(3):217-43.

61. Lawson AE. Hypothetico-deductive Method. In: Gunstone R, éditeur. Encyclopedia of Science Education [Internet]. Dordrecht: Springer Netherlands; 2021 [cité 18 mai 2022]. p. 1-2. Disponible sur: https://doi.org/10.1007/978-94-007-6165-0_260-1

62. Monino JL, Sedkaoui S. Big Data, Open Data et valorisation des données. 2016.

63. Déclaration des Droits de l'Homme et du Citoyen de 1789 - Légifrance [Internet]. [cité 23 juill 2022]. Disponible sur: https://www.legifrance.gouv.fr/contenu/menu/droit-national-en-vigueur/constitution/declaration-des-droits-de-l-homme-et-du-citoyen-de-1789

64. Goëta S, Mabi C. L'open data peut-il (encore) servir les citoyens ? Mouvements. 2014;79(3):81-91.

65. Plan d'action G8 sur l'ouverture des données publiques [Internet]. [cité 23 juill 2022]. Disponible sur: https://www.numerique.gouv.fr/actualites/plan-daction-g8-sur-louverture-des-donnees-publiques/

66. Goeta S. Instaurer des données, instaurer des publics : une enquête sociologique dans les coulisses de l'open data [Internet] [phdthesis]. Télécom ParisTech; 2016 [cité 23 juill 2022]. Disponible sur: https://pastel.archives-ouvertes.fr/tel-01458098

67. Rebouillat V. Le partage des données vu par les chercheurs : une approche par la valeur. Enjeux Inf Commun. 2021;22/1(1):35-53.

68. Borgman CL. Qu'est-ce que le travail scientifique des données ? : Big data, little data, no data [Internet]. Qu'est-ce que le travail scientifique des données ? : Big data, little data, no data. Marseille: OpenEdition Press; 2020 [cité 11 août 2022]. 420 p. (Encyclopédie numérique). Disponible sur: http://books.openedition.org/oep/14692

69. Jacquemin B, Schöpfel J, Fabre R. Libre accès et données de recherche. De l'utopie à l'idéal réaliste. Études Commun Lang Inf Médiations. 1 juin 2019;(52):11-26.

70. OECD. Principes et lignes directrices de l'OCDE pour l'accès aux données de la recherche financée sur fonds publics [Internet]. Paris: Organisation for Economic Co-operation and Development; 2007 [cité 13 août 2022]. Disponible sur: https://www.oecd-ilibrary.org/science-and-technology/oecd-principles-and-guidelines-for-access-to-research-data-from-public-funding_9789264034020-en-fr?mlang=fr

71. Directive (EU) 2019/1024 on open data and the re-use of public sector information – European Sources Online [Internet]. [cité 15 août 2022]. Disponible sur: https://www.europeansources.info/record/directive-eu-2019-1024-on-open-data-and-the-re-use-of-public-sector-information/

72. EUROPE 2020 A strategy for smart, sustainable and inclusive growth [Internet]. 2010. Disponible sur: https://eur-lex.europa.eu/legal-content/en/ALL/?uri=CELEX%3A52010DC2020

73. Riding the Wave. How Europe can gain from the rising tide of scientific data, [Internet]. FOSTER FACILITATE OPEN SCIENCE TRAINING FOR EUROPEAN RESEARCH. [cité 16 août 2022]. Disponible sur: https://www.fosteropenscience.eu/content/riding-wave-how-europe-can-gain-rising-tide-scientific-data

74. COMMUNICATION DE LA COMMISSION AU PARLEMENT EUROPÉEN, AU
CONSEIL, AU COMITÉ ÉCONOMIQUE ET SOCIAL EUROPÉEN ET AU COMITÉ
DES RÉGIONS
Un partenariat renforcé pour l'excellence et la croissance dans l'Espace européen de la
recherche [Internet]. 2012. Disponible sur: https://eur-lex.europa.eu/legal-content/FR/TXT/?uri=CELEX:52012DC0392

75. Guidelines on Open Access to Scientific Publications and Research Data in Horizon 2020. [Internet]. OpenAIRE. [cité 16 août 2022]. Disponible sur: https://www.openaire.eu/guidelines-on-open-access-to-scientific-publications-and-research-data-in-horizon-2020

76. FAIR Principles [Internet]. GO FAIR. [cité 27 mars 2020]. Disponible sur: https://www.go-fair.org/fair-principles/

77. Wilkinson MD, Dumontier M, Aalbersberg IjJ, Appleton G, Axton M, Baak A, et al. The FAIR Guiding Principles for scientific data management and stewardship. Sci Data. 15 mars 2016;3(1):160018.

78. Signature d'une déclaration conjointe en faveur de la science ouverte par un réseau d'agences françaises de financement de la recherche [Internet]. Agence nationale de la recherche. [cité 11 août 2022]. Disponible sur: https://anr.fr/fr/actualites-de-lanr/details/news/signature-dune-declaration-conjointe-en-faveur-de-la-science-ouverte-par-un-reseau-dagences-franc/

79. Jones S. Developments in Research Funder Data Policy. Int J Digit Curation. 12 mars 2012;7(1):114-25.

80. Increasing Access to the Results of Federally Funded Science [Internet]. whitehouse.gov. 2016 [cité 11 août 2022]. Disponible sur: https://obamawhitehouse.archives.gov/blog/2016/02/22/increasing-access-results-federally-funded-science

81. Dissemination and Sharing of Research Results | NSF - National Science Foundation [Internet]. [cité 11 août 2022]. Disponible sur: https://www.nsf.gov/bfa/dias/policy/dmp.jsp

82. Kiley R, Peatfield T, Hansen J, Reddington F. Data Sharing from Clinical Trials — A Research Funder's Perspective. N Engl J Med. 16 nov 2017;377(20):1990-2.

83. Bauchner H, Golub RM, Fontanarosa PB. Data Sharing: An Ethical and Scientific Imperative. JAMA. mars 2016;22;315(12):1237–9.

84. Chopra SS. Industry Funding of Clinical Trials: Benefit or Bias? JAMA. 2 juill 2003;290(1):113-4.

85. Krumholz HM, Gross CP, Blount KL, Ritchie JD, Hodshon B, Lehman R, et al. Sea Change in Open Science and Data Sharing: Leadership by Industry. Circ Cardiovasc Qual Outcomes. juill 2014;7(4):499-504.

86. Tal-Socher M, Ziderman A. Data sharing policies in scholarly publications: interdisciplinary comparisons. Prometheus [Internet]. 1 juin 2020 [cité 24 août 2022]; Disponible sur: https://www.scienceopen.com/hosted-document?doi=10.13169/prometheus.36.2.0116

87. Rousi AM, Laakso M. Journal research data sharing policies: a study of highly-cited journals in neuroscience, physics, and operations research. Scientometrics. 1 juill 2020;124(1):131-52.

88. Huh S. Recent trends in medical journals' data sharing policies and statements of data availability. Arch Plast Surg. nov 2019;46(6):493-7.

89. Taichman DB, Sahni P, Pinborg A, Peiperl L, Laine C, James A, et al. Data Sharing Statements for Clinical Trials: A Requirement of the International Committee of Medical Journal Editors. PLOS Med. 5 juin 2017;14(6):e1002315.

90. Hrynaszkiewicz I, Busch S, Cockerill MJ. Licensing the future: report on BioMed Central's public consultation on open data in peer-reviewed journals. BMC Res Notes. déc 2013;6(1):318, 1756-0500-6-318.

91. Poline JB. From data sharing to data publishing. MNI Open Res. 31 janv 2019;2:1.

92. Science C for O. Registered Reports [Internet]. [cité 17 août 2022]. Disponible sur: https://www.cos.io/initiatives/registered-reports

93. Science C for O. New Measure Rates Quality of Research Journals' Policies to Promote Transparency and Reproducibility [Internet]. [cité 17 août 2022]. Disponible sur: https://www.cos.io/about/news/new-measure-rates-quality-research-journals-policies-promote-transparency-and-reproducibility

94. Read the Declaration (Français) [Internet]. DORA. [cité 19 août 2022]. Disponible sur: https://sfdora.org/read/read-the-declaration-french/

95. Les Principes de Hong Kong : promouvoir l'intégrité de la recherche dans l'évaluation des chercheurs [Internet]. [cité 19 août 2022]. Disponible sur: https://www.ouvrirlascience.fr/les-principes-de-hong-kong-promouvoir-lintegrite-de-la-recherche-dans-levaluation-des-chercheurs

96. Prost H, Schöpfel J. Les entrepôts de données en sciences de l'information et de la communication (SIC). Une étude empirique. Études Commun Lang Inf Médiations. 1 juin 2019;(52):71-98.

97. Pampel H, Kindling M. Le potentiel des infrastructures d'information pour les données de la recherche. Études Commun Lang Inf Médiations. 1 juin 2019;(52):27-50.

98. Ohmann C, Banzi R, Canham S, Battaglia S, Matei M, Ariyo C, et al. Sharing and reuse of individual participant data from clinical trials: principles and recommendations. BMJ Open. 14 déc 2017;7(12):e018647.

99. Kalkman S, Delden J van, Banerjee A, Tyl B, Mostert M, Thiel G van. Patients' and public views and attitudes towards the sharing of health data for research: a narrative review of the empirical evidence. J Med Ethics. 1 janv 2022;48(1):3-13.

100. Mello MM, Lieou V, Goodman SN. Clinical Trial Participants' Views of the Risks and Benefits of Data Sharing. N Engl J Med. 7 juin 2018;378(23):2202-11.

101. Naudet F, Sakarovitch C, Janiaud P, Cristea I, Fanelli D, Moher D, et al. Data sharing and reanalysis of randomized controlled trials in leading biomedical journals with a full data sharing policy: survey of studies published in The BMJ and PLOS Medicine. BMJ. 13 2018;360:k400.

102. Goldacre B, Lane S, Mahtani KR, Heneghan C, Onakpoya I, Bushfield I, et al. Pharmaceutical companies' policies on access to trial data, results, and methods: audit study. BMJ. 26 juill 2017;358:j3334.

103. Miller J, Ross JS, Wilenzick M, Mello MM. Sharing of clinical trial data and results reporting practices among large pharmaceutical companies: cross sectional descriptive study and pilot of a tool to improve company practices. BMJ. 10 juill 2019;366:l4217.

104. DeVito NJ, French L, Goldacre B. Noncommercial Funders' Policies on Trial Registration, Access to Summary Results, and Individual Patient Data Availability. JAMA. 24 avr 2018;319(16):1721-3.

105. Vazquez E, Gouraud H, Naudet F, Gross CP, Krumholz HM, Ross JS, et al. Characteristics of available studies and dissemination of research using major clinical data sharing platforms. Clin Trials. 1 déc 2021;18(6):657-66.

106. Bauchner H, Golub RM, Fontanarosa PB. Data Sharing: An Ethical and Scientific Imperative. JAMA. 22 mars 2016;315(12):1237-9.

107. Nosek BA, Alter G, Banks GC, Borsboom D, Bowman SD, Breckler SJ, et al. Promoting an open research culture. Science. 26 juin 2015;348(6242):1422-5.

108. Tsukuba Communiqué(G7 Science and Technology Ministers' Meeting in Tsukuba, Ibaraki) [Internet]. [cité 27 mars 2020]. Disponible sur: https://www8.cao.go.jp/cstp/english/others/communique_en.html

109. Taichman DB, Sahni P, Pinborg A, Peiperl L, Laine C, James A, et al. Data Sharing Statements for Clinical Trials: A Requirement of the International Committee of Medical Journal Editors. JAMA. 27 2017;317(24):2491-2.

110. Tudur Smith C, Nevitt S, Appelbe D, Appleton R, Dixon P, Harrison J, et al. Resource implications of preparing individual participant data from a clinical trial to share with external researchers. Trials. 17 2017;18(1):319.

111. Goldacre B, Lane S, Mahtani KR, Heneghan C, Onakpoya I, Bushfield I, et al. Pharmaceutical companies' policies on access to trial data, results, and methods: audit study. BMJ. 26 juill 2017;358:j3334.

112. Miller J, Ross JS, Wilenzick M, Mello MM. Sharing of clinical trial data and results reporting practices among large pharmaceutical companies: cross sectional descriptive study and pilot of a tool to improve company practices. BMJ. 10 2019;366:l4217.

113. DeVito NJ, French L, Goldacre B. Noncommercial Funders' Policies on Trial Registration, Access to Summary Results, and Individual Patient Data Availability. JAMA. 24 avr 2018;319(16):1721-3.

114. Research Funders' Open Access Policies - v2.sherpa [Internet]. [cité 27 mars 2020]. Disponible sur: https://v2.sherpa.ac.uk/juliet/

115. Membership [Internet]. [cité 27 mars 2020]. Disponible sur: https://www.efpia.eu/about-us/membership/

116. Members | PhRMA [Internet]. [cité 27 mars 2020]. Disponible sur: https://www.phrma.org/about/members

117. Our Membership – IFPMA [Internet]. [cité 27 mars 2020]. Disponible sur: https://www.ifpma.org/who-we-are/our-membership/

118. Annuaire des entreprises adhérentes | Leem [Internet]. [cité 27 mars 2020]. Disponible sur: https://www.leem.org/annuaire-des-entreprises-adherentes

119. s100-2018_01scrip-100_league-table_online.pdf [Internet]. [cité 27 mars 2020]. Disponible sur: https://scrip.pharmaintelligence.informa.com/-/media/editorial/scrip-100/2018/league-table/s100-2018_01scrip-100_league-table_online.pdf?la=en&hash=DEEA854FEE9CB726831AB413DA04645C353C9223

120. World Bank Open Data | Data [Internet]. [cité 27 mars 2020]. Disponible sur: https://data.worldbank.org/

121. OSF | POLITIQUES DE PARTAGE DE DONNEES DES FINANCEURS DES ESSAIS CLINIQUES RANDOMISES EN FRANCE [Internet]. [cité 27 mars 2020]. Disponible sur: https://osf.io/mr5hx/

122. DeVito NJ, Bacon S, Goldacre B. Compliance with legal requirement to report clinical trial results on ClinicalTrials.gov: a cohort study. Lancet Lond Engl. 01 2020;395(10221):361-9.

123. PillerJan. 13 C, 2020, Am 11:00. FDA and NIH let clinical trial sponsors keep results secret and break the law [Internet]. Science | AAAS. 2020 [cité 27 mars 2020]. Disponible sur: https://www.sciencemag.org/news/2020/01/fda-and-nih-let-clinical-trial-sponsors-keep-results-secret-and-break-law

124. Bergeris A, Tse T, Zarin DA. Trialists' Intent to Share Individual Participant Data as Disclosed at ClinicalTrials.gov. JAMA. 23 janv 2018;319(4):406-8.

125. Longo DL, Drazen JM. Data Sharing. N Engl J Med. 21 janv 2016;374(3):276-7.

126. Hopkins AM, Rowland A, Sorich MJ. Data sharing from pharmaceutical industry sponsored clinical studies: audit of data availability. BMC Med. 28 2018;16(1):165.

127. Noncommercial Funders' Policies on Trial Registration, Access to Summary Results, and Individual Patient Data Availability. - PubMed - NCBI [Internet]. [cité 27 mars 2020]. Disponible sur: https://www.ncbi.nlm.nih.gov/pubmed/29710154

128. icmje-recommendations.pdf [Internet]. [cité 27 mars 2020]. Disponible sur: http://www.icmje.org/icmje-recommendations.pdf

129. EFPIA and PhRMA release joint principles for responsible clinical trial data sharing to benefit patients [Internet]. [cité 27 mars 2020]. Disponible sur: https://www.efpia.eu/news-events/the-efpia-view/statements-press-releases/130724-efpia-and-phrma-release-joint-principles-for-responsible-clinical-trial-data-sharing-to-benefit-patients/

130. Tenopir C, Dalton ED, Allard S, Frame M, Pjesivac I, Birch B, et al. Changes in Data Sharing and Data Reuse Practices and Perceptions among Scientists Worldwide. PLoS ONE [Internet]. 26 août 2015;10(8). Disponible sur: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4550246/

131. Sayogo DS, Pardo TA. Exploring the determinants of scientific data sharing: Understanding the motivation to publish research data. Gov Inf Q. 1 janv 2013;30:S19-31.

132. Taichman DB, Sahni P, Pinborg A, Peiperl L, Laine C, James A, et al. Data Sharing Statements for Clinical Trials: A Requirement of the International Committee of Medical Journal Editors. JAMA. 27 2017;317(24):2491-2.

133. Strom BL, Buyse ME, Hughes J, Knoppers BM. Data Sharing - Is the Juice Worth the Squeeze? N Engl J Med. 27 oct 2016;375(17):1608-9.

134. Data, software and materials management and sharing policy - Grant Funding [Internet]. Wellcome. [cité 8 oct 2022]. Disponible sur: https://wellcome.org/grant-funding/guidance/data-software-materials-management-and-sharing-policy

135. APMnews - L'Inserm et le CNRS appelés à améliorer la transparence entourant leurs essais cliniques [Internet]. [cité 20 juin 2019]. Disponible sur: https://www.apmnews.com/nostory.php?uid=68878&objet=328604.

136. Le Plan national pour la science ouverte : les résultats de la recherche scientifique ouverts à tous, sans entrave, sans délai, sans paiement - Ministère de l'Enseignement supérieur, de la Recherche et de l'Innovation [Internet]. 2018 [cité 20 juin 2019]. Disponible sur: http://www.enseignementsup-recherche.gouv.fr/cid132529/le-plan-national-pour-la-science-ouverte-les-resultats-de-la-recherche-scientifique-ouverts-a-tous-sans-entrave-sans-delai-sans-paiement.html

137. OSF | POLITIQUES DE PARTAGE DE DONNEES DES FINANCEURS DES ESSAIS CLINIQUES RANDOMISES EN FRANCE [Internet]. [cité 9 oct 2019]. Disponible sur: https://osf.io/mr5hx/

138. R Core Team RF for SC. R: A Language and Environment for Statistical Computing [Internet]. Vienna, Austria; 2018 [cité 21 juin 2019]. Disponible sur: https://www.r-project.org/

139. Research Funders' Open Access Policies - v2.sherpa [Internet]. [cité 9 oct 2019]. Disponible sur: https://v2.sherpa.ac.uk/juliet/

140. Nightingale A. Library: Data Management Plans: Other Major Funder Requirements [Internet]. [cité 9 oct 2019]. Disponible sur: //library.bath.ac.uk/research-data/data-management-plans/funder-requirements

141. European Medecines Agency. European Medicines Agency policy on publication of clinical data for medicinal products for human use. 2019.

142. Rathi V, Dzara K, Gross CP, Hrynaszkiewicz I, Joffe S, Krumholz HM, et al. Sharing of clinical trial data among trialists: a cross sectional survey. BMJ [Internet]. 20 nov 2012 [cité 30 déc 2019];345. Disponible sur: https://www.bmj.com/content/345/bmj.e7570

143. Taichman DB, Backus J, Baethge C, Bauchner H, De Leeuw PW, Drazen JM, et al. Editorial-Sharing Clinical Trial Data: A Proposal from the International Committee of Medical Journal Editors. Ethiop J Health Sci. 21 janv 2016;26(1):2.

144. Sydes MR, Johnson AL, Meredith SK, Rauchenberger M, South A, Parmar MK. Sharing data from clinical trials: the rationale for a controlled access approach. Trials. 23 mars 2015;16(1):104.

145. Moher D, Naudet F, Cristea IA, Miedema F, Ioannidis JPA, Goodman SN. Assessing scientists for hiring, promotion, and tenure. PLOS Biol. 29 mars 2018;16(3):e2004089.

146. Demotes-Mainard J, Cornu C, Guérin A, Bertoye PH, Boidin R, Bureau S, et al. How the new European data protection regulation affects clinical research and recommendations? Therapies. 1 févr 2019;74(1):31-42.

147. Mello MM, Lieou V, Goodman SN. Clinical Trial Participants' Views of the Risks and Benefits of Data Sharing. N Engl J Med. 6 juin 2018;378(23):2202-11.

148. Royal Society Open Science : Registered reports [Internet]. Royal Society Open Science. [cité 4 oct 2022]. Disponible sur: https://royalsocietypublishing.orgnull?doi=10.1098%2Frsos&publicationCode=rsos

149. Goodman SN, Fanelli D, Ioannidis JPA. What does research reproducibility mean? Sci Transl Med. 01 2016;8(341):341ps12.

150. Challenges in irreproducible research [Internet]. Nature. [cité 21 avr 2020]. Disponible sur: https://www.nature.com/collections/prbfkwmwvz

151. Ioannidis JPA. Why most published research findings are false. PLoS Med. août 2005;2(8):e124.

152. Collaboration OS. Estimating the reproducibility of psychological science. Science [Internet]. 28 août 2015 [cité 21 avr 2020];349(6251). Disponible sur: https://science.sciencemag.org/content/349/6251/aac4716

153. Begley CG, Ioannidis JPA. Reproducibility in science: improving the standard for basic and preclinical research. Circ Res. 2 janv 2015;116(1):116-26.

154. Florian N, Moher D, Christian O, Edith M. Status of sharing of Individual Participant Data from clinical trials, use of shared data and impact of research outputs of sharing data: a scoping review protocol. 12 sept 2018 [cité 3 juin 2020]; Disponible sur: https://osf.io/pb8cj/

155. Woodhead M. 80% of China's clinical trial data are fraudulent, investigation finds. BMJ. 5 oct 2016;355:i5396.

156. Noury JL, Nardo JM, Healy D, Jureidini J, Raven M, Tufanaru C, et al. Restoring Study 329: efficacy and harms of paroxetine and imipramine in treatment of major depression in adolescence. BMJ [Internet]. 16 sept 2015 [cité 21 avr 2020];351. Disponible sur: https://www.bmj.com/content/351/bmj.h4320

157. Ebrahim S, Sohani ZN, Montoya L, Agarwal A, Thorlund K, Mills EJ, et al. Reanalyses of randomized clinical trial data. JAMA. 10 sept 2014;312(10):1024-32.

158. WHO | Joint statement on public disclosure of results from clinical trials [Internet]. WHO. [cité 21 avr 2020]. Disponible sur: http://www.who.int/ictrp/results/jointstatement/en/

159. Navar AM, Pencina MJ, Rymer JA, Louzao DM, Peterson ED. Use of Open Access Platforms for Clinical Trial Data. JAMA. 22 mars 2016;315(12):1283-4.

160. Home [Internet]. Agence nationale de la recherche. [cité 21 avr 2020]. Disponible sur: https://anr.fr/en/?tx_anrskin%5Bprofile%5D=22&cHash=b279d4f95d062344c2d6993de2c8f288+-6863+union+all+select+CONCAT(0x3a6f79753a,0x424476487769756 9706b,0x3a70687a3a)%23

161. Plesser HE. Reproducibility vs. Replicability: A Brief History of a Confused Terminology. Front Neuroinformatics [Internet]. 18 janv 2018;11. Disponible sur: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5778115/

162. OSF [Internet]. [cité 21 avr 2020]. Disponible sur: https://osf.io/

163. Castillon G, Castilloux AM, Moride Y. Development of Standards for Online Repositories. 2018; Disponible sur: https://wellcome.figshare.com/articles/Development_of_International_Standards_for_Online_Repositories/5897614

164. Banzi R, Canham S, Kuchinke W, Krleza-Jeric K, Demotes-Mainard J, Ohmann C. Evaluation of repositories for sharing individual-participant data from clinical studies. Trials. 15 mars 2019;20(1):169.

165. WHO | Medical Device – Full Definition [Internet]. WHO. [cité 21 avr 2020]. Disponible sur: http://www.who.int/medical_devices/full_deffinition/en/

166. Team RC. R: A language and environment for statistical computing. 2013;

167. Hume S, Chow A, Evans J, Malfait F, Chason J, Wold JD, et al. CDISC SHARE, a Global, Cloud-based Resource of Machine-Readable CDISC Standards for Clinical and Translational Research. AMIA Jt Summits Transl Sci Proc AMIA Jt Summits Transl Sci. 2018;2017:94-103.

168. Cro S, Forbes G, Johnson NA, Kahan BC. Evidence of unexplained discrepancies between planned and conducted statistical analyses: a review of randomised trials. BMC Med. 29 mai 2020;18(1):137.

169. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. Introduction to meta-analysis. John Wiley & Sons; 2011.

170. Siebert M, Gaba J, Renault A, Laviolle B, Locher C, Moher D, et al. Data-sharing and re-analysis for main studies assessed by the European Medicines Agency—a cross-sectional study on European Public Assessment Reports. BMC Med. 20 mai 2022;20(1):177.

171. Ebrahim S, Sohani ZN, Montoya L, Agarwal A, Thorlund K, Mills EJ, et al. Reanalyses of Randomized Clinical Trial Data. JAMA. 10 sept 2014;312(10):1024-32.

172. Bergeat D, Lombard N, Gasmi A, Le Floch B, Naudet F. Data Sharing and Reanalyses Among Randomized Clinical Trials Published in Surgical Journals Before and After Adoption of a Data Availability and Reproducibility Policy. JAMA Netw Open. 2 juin 2022;5(6):e2215209.

173. Kochhar S, Knoppers B, Gamble C, Chant A, Koplan J, Humphreys GS. Clinical trial data sharing: here's the challenge. BMJ Open. 1 août 2019;9(8):e032334.

174. Rathi V, Dzara K, Gross CP, Hrynaszkiewicz I, Joffe S, Krumholz HM, et al. Sharing of clinical trial data among trialists: a cross sectional survey. BMJ. 20 nov 2012;345:e7570.

175. Mello MM, Lieou V, Goodman SN. Clinical Trial Participants' Views of the Risks and Benefits of Data Sharing. N Engl J Med. 07 2018;378(23):2202-11.

176. Wellcome Trust. Sharing research data to improve public health statement [Internet]. Wellcome. [cité 18 sept 2022]. Disponible sur: https://wellcome.org/what-we-do/our-work/sharing-research-data-improve-public-health-full-joint-statement-funders-health

177. Waithira N, Mutinda B, Cheah PY. Data management and sharing policy: the first step towards promoting data sharing. BMC Med. 17 avr 2019;17(1):80.

178. Gaba JF, Siebert M, Dupuy A, Moher D, Naudet F. Funders' data-sharing policies in therapeutic research: A survey of commercial and non-commercial funders. PLOS ONE. 20 août 2020;15(8):e0237464.

179. Rollando P, Parc C, Naudet F, Gaba JF. Les politiques de partage de données des financeurs d'essais cliniques en France. Thérapie. nov 2020;75(6):527-36.

180. Siebert M, Gaba JF, Caquelin L, Gouraud H, Dupuy A, Moher D. Data-sharing recommendations in biomedical journals and randomised controlled trials: an audit of journals following the ICMJE recommendations. BMJ Open. 1 juin 2020;2020;10(5):e038887.

181. Li R, von Isenburg M, Levenstein M, Neumann S, Wood J, Sim I. COVID-19 trials: declarations of data sharing intentions at trial registration and at publication. Trials. 18 févr 2021;22(1):153.

182. Larson K, Sim I, von Isenburg M, Levenstein M, Rockhold F, Neumann S, et al. COVID-19 interventional trials: Analysis of data sharing intentions during a time of pandemic. Contemp Clin Trials. 1 avr 2022;115:106709.

183. Duan Y, Luo J, Zhao L, Zhang X, Miao J, Moher D, et al. Reporting and data sharing level for COVID-19 vaccine trials: A cross-sectional study. eBioMedicine [Internet]. 1 avr 2022 [cité 21 sept 2022];78. Disponible sur: https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(22)00146-3/fulltext

184. Pasquetto IV, Randles BM, Borgman CL. On the Reuse of Scientific Data. 22 mars 2017 [cité 21 sept 2022]; Disponible sur: https://escholarship.org/uc/item/4xf018wx

185. Naudet F, Siebert M, Pellen C, Gaba J, Axfors C, Cristea I, et al. Medical journal requirements for clinical trial data sharing: Ripe for improvement. PLOS Med. 25 oct 2021;18(10):e1003844.

186. Pellen C, Caquelin L, Jouvance-Le Bail A, Gaba J, Vérin M, Moher D, et al. Intent to share Annals of Internal Medicine's trial data was not associated with data re-use. J Clin Epidemiol. sept 2021;137:241-9.

187. Mbuagbaw L, Foster G, Cheng J, Thabane L. Challenges to complete and useful data sharing. Trials. 14 févr 2017;18(1):71.

188. NOT-OD-21-013: Final NIH Policy for Data Management and Sharing [Internet]. [cité 21 sept 2022]. Disponible sur: https://grants.nih.gov/grants/guide/notice-files/NOT-OD-21-013.html

189. Kozlov M. NIH issues a seismic mandate: share data publicly. Nature. 16 févr 2022;602(7898):558-9.

190. Pasquetto I. PhD Dissertation - From Open Data to Knowledge Production: Biomedical Data Sharing and Unpredictable Data Reuses. 11 nov 2018 [cité 21 sept 2022]; Disponible sur: https://escholarship.org/uc/item/1sx7v77r

191. Rebouillat V. Ouverture des données de la recherche : de la vision politique aux pratiques des chercheurs [Internet] [phdthesis]. Conservatoire national des arts et metiers - CNAM; 2019 [cité 21 sept 2022]. Disponible sur: https://tel.archives-ouvertes.fr/tel-02447653

192. OSEC 2022. Appel de Paris – OSEC 2022 [Internet]. [cité 24 sept 2022]. Disponible sur: https://osec2022.eu/fr/appel-de-paris/

193. Time to recognize authorship of open data. Nature. 6 avr 2022;604(7904):8-8.

194. Ateliers de la donnée : nouvelle étape dans la construction de l'écosystème Recherche Data Gouv [Internet]. [cité 21 sept 2022]. Disponible sur: https://www.ouvrirlascience.fr/ateliers-de-la-donnee-nouvelle-etape-dans-la-construction-de-lecosysteme

195. Global coalition to accelerate COVID-19 clinical research in resource-limited settings. The Lancet. 25 avr 2020;395(10233):1322-5.

196. Bootun R, Belramman A, Bolton-Saghdaoui L, Lane TRA, Riga C, Davies AH. Randomized Controlled Trial of Compression After Endovenous Thermal Ablation of Varicose Veins (COMETA Trial). Ann Surg. 1 févr 2021;273(2):232-9.

197. Why most psychological research findings are not even wrong - Scheel - 2022 - Infant and Child Development - Wiley Online Library [Internet]. [cité 8 oct 2022]. Disponible sur: https://onlinelibrary.wiley.com/doi/full/10.1002/icd.2295

198. Munafò MR, Davey Smith G. Robust research needs many lines of evidence. Nature. janv 2018;553(7689):399-401.

199. Lawlor DA, Tilling K, Davey Smith G. Triangulation in aetiological epidemiology. Int J Epidemiol. 1 déc 2016;45(6):1866-86.

200. Hammerton G, Munafò MR. Causal inference with observational data: the need for triangulation of evidence. Psychol Med. mars 2021;51(4):563-78.

ANNEXES

Annexe 1 : Liste des financeurs analysés

ANR	Fondation Paralysie Cérébrale
DGOS	Fondation pour la Recherche sur les AVC
Ligue contre le cancer	IRME
Vaincre la Mucoviscidose	Alsace contre le cancer/ARECOTH
INCA	Fondation Visio
Hospices Civils de Lyon	Association Hubert Gouin
Fondation APICIL	FRHTA
GIRCI EST	Association Connaitre les Syndromes Cerebelleux
GIRCI GRAND OUEST	SFC
Fondation ARSEP	SFA
FRC	Fondation Motrice
Fondation de l'Avenir	GIRCI NORD OUEST
Vaincre Alzheimer	Cancéropôle Nord Ouest
ARSLA	Agence Française d'urologie / GETUG
FFRD	Fondation Cœur et Recherche
Cancéropôle EST	Inserm

Web appendix number 1

Letter to the Sponsor:

Dear XXX,

I am a PhD student at Rennes 1 University working in Rennes Clinical Research Investigation Center (CIC Inserm 1414) under the supervision of Florian Naudet (MD, PhD). My research team and I are interested in re-analyzing the primary outcomes of clinical trials sharing their data on major data-sharing platforms.

Your study 'XXXX' is one such trial and has been selected for re-analysis. Therefore, I would greatly appreciate if you could share the data from the trial with us: 1) raw data /IPD 2) data analysis plan, 3) unpublished and/or published study protocol with its dated amendments 4) / all the following dates: date of the last visit of the last patient, date of database lock (if available) and date of study unblinding 5) dates of unpublished and/or published (scientific article) study reports.

Sharing in the form of the Standard Tabulation Data Model (STDM) developed by the Clinical Data International Standard Consortium is welcome but not mandatory.

If you cannot share any of these data, please indicate the reason for not sharing.

Our study is pre-registered and can be accessed on the Open Science Framework: XXXX.

Yours Sincerely,

XXXX,

PhD Student,

Univ Rennes, CHU Rennes, Inserm, CIC 1414 (Centre d'Investigation Clinique de Rennes), 35000 Rennes, France

Web Appendix Number 2

Table of Study Characteristics that will be extracted

Study Characteristic
Year of publication (YYYY)
Authors' Name
Country of study location
PMID
Trial Type (Cluster, Parallel, Cross-over)
Trial Design (Superiority or non-inferiority / head to head or another design (factorial))
Bias Assessment Selection bias: Random sequence generation Selection bias: Allocation concealment Performance Bias: Blinding of staff and participant Detection Bias: Blinding of outcome assessment Attrition Bias: Incomplete outcome data Reporting Bias: Selective reporting Other sources of bias
Number of Participants
Number of Groups
Percentage of women
Intervention Drug
Comparator drug (Placebo or another drug)
Medical specialty
Primary Endpoint Definition
Study Duration (Years, Standard Deviation)
Duration of exposure (Years, Standard Deviation)
Sponsorship No Device provided Intervention provided Drug provided Drug and some financial support provided Partial financial support provided Total financial support provided

Web appendix number 3:

List of excluded repositories

	Names of repositories	**Reasons for exclusion**

1	B2Share	Not focused on clinical trials alone
2	BioGrid Australia Limited	Not focused on clinical trials alone
3	Biomedical Informatics Research Network	Not operating
4	CancerData.Org	Disease-specific
5	Critical Path Institute	Disease-specific
6	Clinical Trials Transformation Initiative	Not focused only on clinical trials
7	DataOne	Not focused on clinical trials alone
8	Drum	Not focused on clinical trials alone
9	Dryad	Not focused on clinical trials alone
10	EASY	Not focused on clinical trials alone
11	Early Breast Cancer Trialists' Collaborative Group	Disease-specific
12	Edinburgh DataShare	Not focused on clinical trials alone
13	Fairsharing	Not focused on clinical trials alone
14	FDA Janus	No access to data allowed
15	Figshare	Not focused on clinical trials alone
16	FreeBird	Disease-specific
17	Global Health Data Exchange	Not focused on clinical trials alone
18	Harvard Dataverse	Not focused on clinical trials alone
19	Health and Medical Care Archive	Not focused on clinical trials alone
20	Henry A. Murray Research Archive at Harvard University	Not focused on clinical trials alone
21	INDEPTH Data Repository	Not focused on clinical trials alone
22	Infectious Diseases Data Observatory	Disease-specific

23	International Severe Acute Respiratory Emerging Infection Consortium	Disease-specific
24	Inter-university Consortium for Political and Social Research	Not focused on clinical trials alone
25	International Stroke Trial Database	Disease-specific
26	ITN Trialshare	Disease-specific
27	Médecins sans frontières	Disease-specific
28	Melanoma MMP	Disease-specific
29	Mendeley Data	Not focused on clinical trials alone
30	National Addiction & HIV Data Archive Program	Disease specific
31	National Archive of Computerized Data on Aging	Disease specific
32	National Archive of Criminal Justice Data	Not focused on clinical trials alone
33	National Center for Biotechnology Information	Not focused on clinical trials alone
34	National Institute of Mental Health Data Archive	Not focused on clinical trials alone

35	NDACAN	Disease-specific
36	National Database for Autism Research (US)	Disease-specific
37	NDCT NIMH	Disease specific
38	Neuroscience Information Framework	Disease specific
39	NIDDK	Disease-specific
40	NIH BioLINCC	Disease-specific
41	NIH NIDA: National Institute of Drug Abuse (US)	Disease-specific
42	Open Science Framework	Not focused on clinical trials alone
43	Population Data British Columbia	Not focused on clinical trials alone
44	ProAct	Disease-specific
45	Project Data Sphere	Disease-specific
46	Reactome	Not focused on clinical trials alone
47	Run My Code	Not focused on clinical trials alone
48	SOAR: Duke Clinical research Institute	Not operating
49	Substance Abuse and Mental Health Data Archive	Disease-specific
50	Swedish National Data Service	Not focused on clinical trials alone
51	Sylvia Lawry Centre	Not operating
52	TBI-IMPACT	Disease-specific

53	The Knowledge Network for Biocomplexity	Not focused on clinical trials alone
54	University of Florida Health Integrated Data Repository	Not focused on clinical trials alone
55	UK Data Archive	Not focused on clinical trials alone
56	UK Data Service	Not focused on clinical trials alone
57	UMIN	Access to data not allowed
58	Worldwide Protein Data Bank	Not focused on clinical trials alone
59	WWARN	Disease -pecific
60	Zenodo	Not focused on clinical trials alone

BMJ Open

Data-sharing recommendations in biomedical journals and randomised controlled trials: an audit of journals following the ICMJE recommendations

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ABSTRACT

Objective To explore the implementation of the International Committee of Medical Journal Editors (ICMJE) data-sharing policy which came into force on 1 July 2018 by ICMJE-member journals and by ICMJE-affiliated journals declaring they follow the ICMJE recommendations.

Design A cross-sectional survey of data-sharing policies in 2018 on journal websites and in data-sharing statements in randomised controlled trials (RCTs).

Setting ICMJE website; PubMed/Medline.

Eligibility criteria ICMJE-member journals and 489 ICMJE-affiliated journals that published an RCT in 2018, had an accessible online website and were not considered as predatory journals according to Beall's list. One hundred RCTs for member journals and 100 RCTs for affiliated journals with a data-sharing policy, submitted after 1 July 2018.

Main outcome measures The primary outcome for the policies was the existence of a data-sharing policy (explicit data-sharing policy, no data-sharing policy, policy merely referring to ICMJE recommendations) as reported on the journal website, especially in the instructions for authors. For RCTs, our primary outcome was the intention to share individual participant data set out in the data-sharing statement.

Results Eight (out of 14; 57%) member journals had an explicit data-sharing policy on their website (three were more stringent than the ICMJE requirements, one was less demanding and four were compliant), five (35%) additional journals stated that they followed the ICMJE requirements, and one (8%) had no policy online. In RCTs published in these journals, there were data-sharing statements in 98 out of 100, with expressed intention to share individual patient data reaching 77 out of 100 (77%; 95% CI 67% to 85%). One hundred and forty-five (out of 489) ICMJE-affiliated journals (30%; 26% to 34%) had an explicit data-sharing policy on their website (11 were more stringent than the ICMJE requirements, 85 were less demanding and 49 were compliant) and 276 (56%; 52% to 61%) merely referred to the ICMJE requirements. In RCTs published in affiliated journals with an explicit data-sharing policy, data-sharing statements were rare (25%), and expressed intentions to share data were found in 22% (15% to 32%).

Conclusion The implementation of ICMJE data-sharing requirements in online journal policies was suboptimal for ICMJE-member journals and poor for ICMJE-affiliated journals. The implementation of the policy was good in member journals and of concern for affiliated journals. We suggest the conduct of continuous audits of medical journal data-sharing policies in the future.

Registration The protocol was registered before the start of the research on the Open Science Framework (https://osf.io/n6whd/).

Strengths and limitations of this study

- This original research is a comprehensive assessment of data-sharing policies based on the International Committee of Medical Journal Editors (ICMJE) recommendations.
- In our approach we focused on both ICMJE-member and ICMJE-affiliated journals.
- Data-sharing policies are set in a fast-changing environment and results obtained today might be outdated in the future.
- One limitation is that we only relied on online information.

INTRODUCTION

In June 2017, the International Committee of Medical Journal Editors (ICMJE) published a statement supporting data-sharing practices for randomised controlled trials (RCTs). For the ICMJE, 'there is an ethical obligation to responsibly share data generated by interventional clinical trials because trial participants have put themselves at risk' with the aim to 'maximize the knowledge gained' from these outstanding studies. The ICMJE policy requires a specific data-sharing statement to be included in each newly submitted paper (and prespecified in study registration) containing clinical trial data, starting 1 July 2018.[1]

Examples of medical journals having a data-sharing policy before this requirement were few. In 2007, the *Annals of Internal Medicine* was the first journal to adopt a policy encouraging data-sharing practices.[2] *The BMJ* adopted a similar policy encouraging data-sharing in 2009,[3] and went further by making it mandatory in 2013 for drugs and devices[4] and for all RCTs in 2015.[5] *PLOS* journals also adopted a strict policy enforcing RCT data-sharing in 2014.[6] No other leading general medical journal has had a specific policy for data-sharing in RCTs.

The ICMJE policy could therefore have an impact on biomedical literature as a whole. At the time of the present research, the ICMJE included two organisations (the US National Library of Medicine and the World Association of Medical Editors) and 14 journals, including leading medical journals such as *The New England Journal of Medicine (NEJM)* and *The Lancet*. In addition, about 5000 affiliated journals follow the ICMJE recommendations.[7] As this policy is now in place, it is important to monitor its implementation both in the ICMJE-member journals and in the ICMJE-affiliated journals. It is also important to assess intentions to share data among RCTs published in the journals implementing a data-sharing policy.

METHODS

The protocol was registered before the start of the research on the Open Science Framework (OSF) (https://osf.io/n6whd/). This study was divided into two parts: a survey of journal data-sharing policies and a survey of published RCTs.

Survey of journal data-sharing policies

Journal eligibility criteria

Two samples of journals were surveyed: the 14 ICMJE-member journals at the time of the present research (*Annals of Internal Medicine*, *British Medical Journal*, *Bulletin of the World Health Organization*, *German Medical Journal*, *Ethiopian Journal of Health Sciences*, *Iranian Journal of Medical Sciences*, *Journal of the American Medical Association*, *Journal of Korean Medical Science*, *New England Journal of Medicine*, *New Zealand Medical Journal*, *PLOS Medicine*, *The Lancet*, *Medical Journal of Chile* and *Danish Medical Journal*) and a sample of ICMJE-affiliated journals listed on the ICMJE website on 1 February 2019. Journals were included if they (1) had medical content; (2) had published at least one RCT in 2018; (3) had published articles in English, German, French, Spanish or Portuguese; (4) had an accessible online website; and (5) were not considered as 'predatory' journals according to Beall's list.[8]

Search strategy for journals

The ICMJE website was consulted to copy the list of all ICMJE-member journals and all 4892 ICMJE-affiliated journals. In cases where an affiliated journal changed its name after registration on the ICMJE website (eg, *Cancer Immunity* changed to *Cancer Immunology Research*), we checked whether the new name was also listed on the ICMJE website. If this was the case, the journal was considered as non-eligible and was marked as 'discontinued'; otherwise it was included.

All 4892 ICMJE-affiliated journals were assessed for eligibility in random order obtained using the R statistical software.[9] The results of the randomisation can be found in the supplementary material on the OSF page.[10] The first 489 journals that met the selection criteria (10% of affiliated journals) were included, enabling us to estimate a proportion of 50% (the worst-case scenario for precision estimates) with a precision (boundaries of the 95% CI) of about ±4.5%.

Journal selection and data extraction

A data extraction sheet and a data extraction explanatory document were developed.[10] Three investigators in charge of data extraction (MS, LC, HG) had a 1-hour training session and completed a pilot data extraction on 10 journals. For each journal, pairs of these investigators independently assessed eligibility (with reasons in case of non-eligibility) and extracted the data on all the outcomes listed in the following sections from each included journal. Disagreements were resolved by consensus or in consultation with a third investigator (FN).

Outcomes describing journal data-sharing policies

Our primary outcome was the existence of a data-sharing policy (specific data-sharing policy, no data-sharing policy or a policy merely referring to ICMJE requirements) as reported on the journal website. This outcome had to be changed from our initial protocol due to non-response to our emails from the sample of ICMJE-affiliated journals and because some email addresses could not be identified. The change took place before any analysis. For journals mentioning a specific data-sharing policy on their website, 'the explicit statement and various features of these policies were collected: the start date of the data-sharing policy, the type of policy: ICMJE compliant, more stringent than required by ICMJE or less demanding than required by ICMJE (for instance, less demanding could mean that there was no obligation for a data-sharing statement, and more stringent could mean that data were to be shared with other researchers). We also noted whether the policy was limited to clinical trials, and furthermore the indication of one or more preferred data-sharing platform (and if so, which ones) and the existence of any sanctions in case of non-compliance with data-sharing (and if so, what they were). Any existing policy demanding trial registration was also extracted (and if there was one, we noted whether it mentioned prospective registration). The following features of the journals were also extracted: indexed on PubMed, International Standard Serial Number (ISSN or print ISSN), number of issues per year, 2017 journal impact factor (JIF), publisher or publishing group, gender of the editor in chief ('men', 'women' and 'both genders represented', if the coeditors in chief were men and women), country of the journal head office, wealth category of the country where the

editorial office is located as defined by the World Bank[11] and the research domain covered by the journal.

Survey of RCTs published in journals with a data-sharing policy

RCT eligibility criteria

Eligible studies were RCTs published after 1 January 2019 in a journal with an explicit data-sharing policy reported on its website and submitted after 1 July 2018. Any RCTs, including cluster trials and cross-over trials, non-inferiority designs and superiority designs, were included. No distinction was made in terms of patients, interventions, comparators or outcomes. We had originally planned to include only phase III studies but realised that this information was not always reported in the publications. Consequently, no distinction in terms of study phase was applied.

Search strategy for RCTs published in journals with a data-sharing policy

ICMJE-member journals were contacted to gather the list of RCTs they published after 1 January 2019. This approach was not used for ICMJE-affiliated journals due to non-response from most of the 14 member journals and because it was not possible to identify an email contact for all these journals. The following search strategy was applied to retrieve all RCTs. For journals indexed on PubMed/Medline, a search algorithm to identify RCTs was developed with the help of a librarian from Rennes 1 University using the Cochrane sensitivity maximising approach[12] and adding further keywords. The exact filter can be found in the supplementary material on the OSF page.[10] For journals not indexed on PubMed, an investigator (MS) screened all articles published after 1 January 2019 to identify RCTs.

All identified RCTs published in ICMJE-member journals with a data-sharing policy were assessed in random order using R.[10] The first 100 that met our selection criteria were included, enabling us to estimate a proportion of 50% (the worst-case scenario for precision estimates) with a precision (boundaries of the 95% CI) of ±9.8%. We followed the same approach to include a second sample of 100 RCTs published in ICMJE-affiliated journals.

RCT selection and data extraction

As for the journal selection procedure, a data extraction sheet and a data extraction explanatory document were developed.[10] Three investigators (MS, LC, JFG) had a 1-hour explanation and were trained via a pilot data extraction performed on 10 RCTs. For each RCT, two of these investigators independently assessed eligibility (giving reasons in case of non-eligibility) and extracted the characteristics listed in the following sections from each included published article. Disagreements were resolved by consensus or in consultation with a third investigator (FN).

Outcomes describing data-sharing statements in published RCTs

For this part of our survey, the primary outcome was the intention to share individual patient data (IPD) expressed by the authors in the data-sharing statement (yes/no/unclear). The latter of the three response options, 'unclear', was recorded if the statement was written in a general tone without specifically mentioning that IPD would be available. Secondary outcomes were trial registrations: the existence of trial registration, prospective trial registration and registration of a data-sharing plan. If the trial report mentioned the existence of a data-sharing plan, we checked whether there was an intention to share data or not. For data-sharing under the secondary outcomes, we checked whether a statement was included in the article, whether the statistical code was shared, whether other data sets than IPD were available and if not whether only parts were available, and lastly whether any other documents were available. Under the section data accessibility, we checked to see whether there was a time restriction for data access, whether it was freely accessible or with restrictions, whether the data could be used for any type of purpose and if not whether there was an aim for data use suggested in the proposal, whether there was a specific access mechanism, and whether data requests were reviewed by an independent committee.

Statistical analysis

All outcomes were reported and described by counts, percentages, means (or medians) and SD (or range) with all the corresponding 95% CIs. If available, verbatim quotes from journal policies were used (qualitative analysis). For ICMJE-affiliated journals, the features of the included journals were compared as part of an exploratory analysis between journals with and without a specific data-sharing policy using univariate logistic regression and multivariate logistic regression (which included covariates identified in univariate analyses at a threshold of $p<0.25$). Due to complete separation observed in our data set, the 'brglm' package in R was used, implementing the bias reduction method developed by Firth.[13] All analyses were conducted using R V.3.4.1. The supplementary material on the OSF page contains our statistical analysis plan.[10]

Changes to the initial protocol

The definition of our primary outcome for journal policies was changed. Indeed, we had initially planned to contact journals with no explicit policy on their website to ask them about the existence of a data-sharing policy. Due to non-response from some of the 14 member journals, and because it was not possible to identify an email contact for all ICMJE-affiliated journals, we decided to rely only on the information presented on the journal websites. Some minor changes were also made. Our selection criteria were simplified so that only one RCT in 2018 was necessary (instead of three over the last 3 years as initially planned). No distinction was made for RCTs in terms of clinical phase. Lastly, we added a secondary

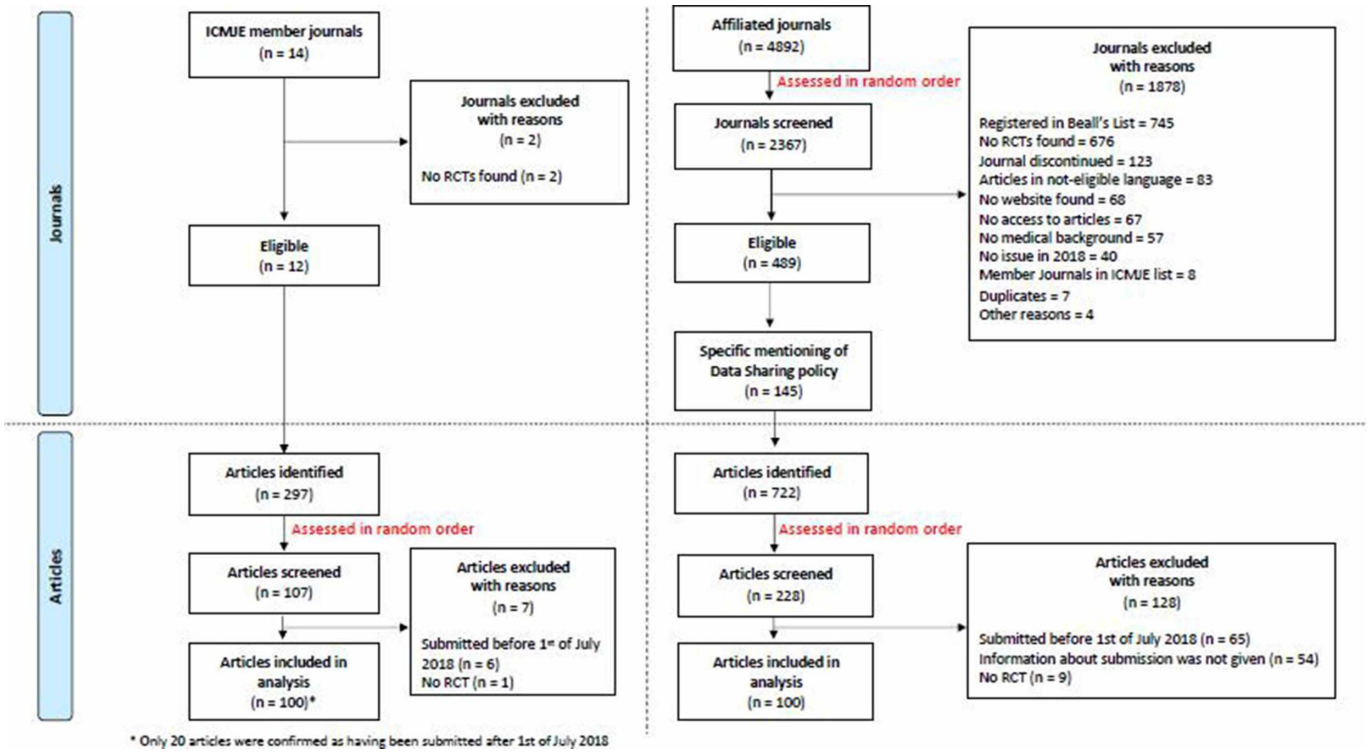

Figure 1 Flow chart of the selection and analysis process for journals and articles. ICMJE, International Committee of Medical Journal Editors; RCT, randomised controlled trial.

outcome, whether or not data requests were reviewed by an independent committee.

Patient and public involvement

We had no established contacts with specific patient groups in this project. No patients were involved in defining the research question or the outcome measures, nor were they involved in the design and implementation of the study. There are no plans to involve patients in the dissemination of results, nor will we disseminate results directly to patients.

RESULTS

Survey of journal data-sharing policies

Journal selection and data extraction

Search for and extraction of eligible journals started on 1 February 2019, ended with a consensus on 11 July 2019, and resulted in 14 ICMJE-member journals and 4892 ICMJE-affiliated journals. Of the affiliated journals, 2367 were randomly screened and 1878 (79%) were excluded, including 745 journals (31% of all screened journals) for which the journal and/or the publisher were listed as 'predatory' on Beall's list. Therefore, 489 ICMJE-affiliated journals were included in analyses as initially planned. The selection process is reported in figure 1.

ICMJE-member journals

The characteristics of the 14 ICMJE-member journals are detailed in table 1.

Twelve of 14 (86%) journals published an RCT in 2018. The *New Zealand Medical Journal* and the *Ethiopian Journal of Health Sciences* did not publish an RCT in 2018. Eight (57%) journals had a specific data-sharing policy on their website: three (38%) of these had a more stringent policy than required by the ICMJE (IPD to be available for *The BMJ* and *PLOS Medicine*, or explicit demands of data for peer review for the *Annals of Internal Medicine*), four were ICMJE-compliant (50%; *NEJM*, *Danish Medical Journal*, *Journal of the American Medical Association* and *The Lancet*), and one (12%; *Journal of Korean Medical Science*) had a less demanding policy than required by the ICMJE that did not require a data-sharing statement but merely encouraged it. Of 14 medical journals, 5 (35%; *Bulletin of the World Health Organization*, *German Medical Journal*, *Ethiopian Journal of Health Sciences*, *Iranian Journal of Medical Sciences and Medical Journal of Chile*) referred to the ICMJE guidelines and 1 (8%; *The New Zealand Medical Journal*) did not have any policy mentioned on its website (its editorial office said that they had no time to clarify this point with us). Only three journals had a data-sharing policy before 2017. The earliest was presented in 2007 by the *Annals of Internal Medicine*, followed by *PLOS Medicine* and *The BMJ* in 2014 and 2015, respectively.

Three journals (out of 14, 21%; *The BMJ*, *PLOS Medicine* and *The Lancet*) indicated specific data-sharing platforms in their policy: Dryad and Mendeley.

For the eight journals with specific data-sharing statements, five referred specifically to clinical trial data, and for the three others it was for all research data submitted.

Sanctions were described in two journals, *PLOS Medicine* and the *Annals of Internal Medicine*: possible rejection of the manuscript if the data were not provided.

Table 1 Characteristics of journal policies for ICMJE-member and ICMJE-affiliated journals

	ICMJE-member journals (n=14)	ICMJE-affiliated journals (n=489)
Type of data-sharing policy		
Explicit	8 (57%)	145 (30%; 26% to 34%)
Not existing	1 (8%)	68 (14%; 11% to 17%)
ICMJE	5 (35%)	276 (56%; 52% to 61%)
Sanctions in non-compliance of data-sharing	2 (14%)	0
Trial registration demanded		
Yes, with a specification that it must be prospective	7 (50%)	178 (37%; 32% to 41%)
Yes, without specification	3 (21%)	142 (29%; 25% to 33%)
Referring to ICMJE	3 (21%)	114 (23%; 20% to 27%)
No	1 (8%)	55 (11%; 9% to 14%)
Issue/year*	16 (12–51)	6 (4–12)
Impact factor 2017†	11.7 (2.7–35.6)	2.4 (1.5–4)

*Not found for two journals; indicated in median and IQR.
†Not found for 258 journals; indicated in median and IQR.
ICMJE, International Committee of Medical Journal Editors.

Except for the *Ethiopian Journal of Health Sciences* and the *Iranian Journal of Medical Sciences*, all journals had their editorial office in high-income countries.

ICMJE-affiliated journals

The characteristics of the 489 ICMJE-affiliated journals are also presented in table 1. Of these journals, 145 (30%; 95% CI 26% to 34%) had a specific data-sharing policy on their website. Two hundred and seventy-six journals (56%; 52% to 61%) merely referred to the ICMJE guidelines, without any specific mention of a data-sharing policy. Sixty-eight (14%; 11% to 17%) had no data-sharing policy and did not allude to the ICMJE in their recommendations. In contrast, 178 (37%; 32% to 41%) required prospective trial registration, 142 (29%; 25% to 33%) asked for trial registration without specifications, 114 (23%; 20% to 27%) referred to the ICMJE, and 55 (11%; 9% to 14%) did not refer to any trial registration.

Among the 145 journals with a specific data-sharing policy, 11 (7%; 4% to 13%) had a more stringent policy than that required by the ICMJE, 49 (34%; 26% to 42%) journals were ICMJE-compliant, and 85 (59%; 50% to 67%) had a less demanding policy than required by the ICMJE that did not explicitly require a data-sharing statement. Nineteen (out of 145; 13%) journals with data-sharing policies referred only to clinical trial data, while for the rest the statement comprised a more general statement. Out of 145 journals, 94 (65%) had no start date found for the policy, 25 (17%) had a policy starting in early 2018 (January and February), and 26 (18%) had a policy starting on 1 July 2018.

One hundred and one (out of 145; 70%) journals indicated a preferred data-sharing platform, with Mendeley (81 journals), Figshare (79 journals) and Dryad (67 journals) being the three most often cited.

Except for the gender of the editor, all features explored in univariate analyses were associated (p<0.25) with the explicit mention of a data-sharing policy on the journal website and were therefore used in the multivariate analyses. Publisher and wealth category of country of journal offices remained associated with the explicit mention of a data-sharing policy in multivariate analysis. The respective adjusted ORs can be found in table 2.

Survey of RCTs published in journals with a data-sharing policy

RCT selection and data extraction

Search for and extraction of eligible RCTs started on 6 August 2019 and ended with a consensus on 26 September 2019. Among the 12 eligible ICMJE-member journals, the *New Zealand Journal of Medicine* and the *Ethiopian Journal of Health Sciences* did not present any RCT in 2018. *PLOS Medicine* and the *Bulletin of the World Health Organization* provided a list of published articles. Two hundred and ninety-seven RCTs published in member journals were found.[10] We could only confirm for 20 articles that they had been submitted after 1 July 2018. For six articles without data-sharing statements in the *NEJM* and *The Lancet*, we were not sure if they were eligible with respect to the submission date. Authors were contacted and we were able to confirm for two journals that they had been submitted before 1 July 2019. These were replaced, as were the four others where doubt persisted. Among the affiliated journals 722 RCTs were identified and were randomly sorted and assessed for eligibility criteria. Figure 1 details the selection process for both ICMJE-member and ICMJE-affiliated journals.

Table 2 Journal characteristics associated with an explicit data-sharing policy

	All journals (n=489)	Journals with an explicit data-sharing policy (n=145)	Journals without an explicit data-sharing policy (n=344)	Univariate analysis OR (95% CI)	P value	Multivariate analysis aOR (95% CI)*	P value
Number of issues per year*							
More than 12 (reference)	17 (4%)	9 (6%)	8 (2%)	–	–	–	–
1–5	241 (49%)	45 (31%)	196 (57%)	0.21 (0.07 to 0.56)	0.002	1 (0.25 to 4.17)	0.83
6–12	229 (47%)	90 (73%)	139 (41%)	0.58 (0.21 to 1.56)	0.28	0.88 (0.25 to 3)	0.99
Journal impact factor							
First quartile (reference) (0.126–1.532)	58 (12%)	20 (14%)	38 (11%)			–	–
Second quartile (1.532–2.388)	58 (12%)	25 (17%)	33 (10%)	1.43 (0.68 to 3.07)	0.35	0.9 (0.35 to 2.32)	0.82
Third quartile (2.388–3.993)	57 (12%)	28 (19%)	29 (8%)	1.81 (0.87 to 3.92)	0.12	0.77 (0.28 to 2.05)	0.59
Fourth quartile (3.993–20.871)	58 (12%)	32 (22%)	26 (8%)	2.3 (1.11 to 5.01)	0.03	1.7 (0.69 to 4.65)	0.26
No impact factor	258 (52%)	40 (28%)	218 (63%)	0.35 (0.19 to 0.67)	0.001	0.52 (0.2 to 1.3)	0.16
Publisher†							
Big output	194 (40%)	66 (45%)	128 (37%)	–	–	–	–
Medium output	39 (8%)	32 (22%)	7 (2%)	8.37 (3.77 to 22.86)	<0.001	3.23 (1.23 to 11.33)	0.02
Small output	39 (8%)	17 (12%)	22 (7%)	1.5 (0.74 to 3.01)	0.25	0.36 (0.08 to 1.09)	0.09
Other	217 (44%)	30 (21%)	187 (54%)	0.31 (0.19 to 0.51)	<0.001	0.35 (0.17 to 0.63)	0.001
Gender of editor							
Men (reference)	403 (82%)	120 (83%)	283 (82%)	–	–	–	–
Women	63 (13%)	16 (11%)	47 (14%)	0.82 (0.43 to 1.46)	0.51	–	–
Both genders represented	23 (5%)	9 (6%)	14 (4%)	1.54 (0.62 to 3.55)	0.33	–	–
Country of editorial office‡							
North America (reference)	114 (24%)	51 (40%)	63 (19%)	–	–	–	–
Asia/Middle East/ Oceania	211 (45%)	22 (17%)	189 (56%)	0.15 (0.08 to 0.26)	<0.001	0.96 (0.4 to 2.25)	0.92
Europe	71 (15%)	16 (12%)	55 (16%)	0.37 (0.18 to 0.7)	0.003	0.48 (0.21 to 1)	0.06
UK	51 (11%)	37 (29%)	14 (4%)	3.2 (1.6 to 6.86)	0.001	1.82 (0.83 to 4.4)	0.15
Other country/region	21 (4%)	2 (2%)	19 (5%)	0.16 (0.02 to 0.53)	0.01	3.01 (0.3 to 19.02)	0.23
Income band of country of editorial office‡							
High income (reference)	270 (58%)	120 (94%)	150 (44%)	–	–	–	–
Upper middle income	88 (19%)	4 (3%)	84 (25%)	0.07 (0.2 to 0.16)	<0.001	0.12 (0.02 to 0.44)	0.002
Lower middle income/ low income	110 (23%)	4 (3%)	106 (31%)	0.05 (0.01 to 0.13)	<0.001	0.09 (0.02 to 0.27)	<0.001
Research domain							
General and internal medicine (reference)	110 (22%)	19 (13%)	91 (26%)	–	–	–	–
Surgery specialty	71 (15%)	23 (16%)	48 (14%)	2.27 (1.14 to 4.67)	0.02	1.47 (0.6 to 3.84)	0.4
Dentistry	30 (6%)	3 (2%)	27 (8%)	0.6 (0.12 to 1.82)	0.41	0.43 (0.04 to 2.02)	0.33
Medical specialty	220 (45%)	75 (52%)	145 (43%)	2.43 (1.41 to 4.47)	0.002	1.12 (0.53 to 2.51)	0.76
Pharmacology and pharmacy	23 (5%)	12 (8%)	11 (3%)	5.1 (2 to 13.84)	<0.001	2.47 (0.66 to 11.29)	0.19
Other specialty	35 (7%)	13 (9%)	22 (6%)	2.82 (1.2 to 6.6)	0.02	1.35 (0.42 to 4.4)	0.6

*Missing data for 2 journals: 1 journal without explicit data-sharing policy and 1 with explicit data-sharing policy.
†Missing data for 21 journals: 4 journals without explicit data-sharing policy and 17 with explicit data-sharing policy.
‡Journals that published over 15 journals in the medical domain: big output >1000 journals, medium output 250–1000 journals, small output <250 journals in publisher repertoire. Other: publishers that did publish under 15 journals in the medical domain.
aOR, adjusted Odds ratio.

Table 3 Characteristics of all published randomised controlled trials included

	ICMJE-member journals (n=100)	ICMJE-affiliated journals (n=100)
Data-sharing statement in article	98 (98%; 92% to 99%)	25 (25%; 17% to 35%)
Intentions to share individual patient data in statement		
Yes	67 (67%; 57% to 76%)	17 (17%; 10% to 26%)
No	21 (21%; 14% to 31%)	3 (3%; 0.1% to 9%)
Unclear	10 (10%; 5% to 18%)	5 (5%; 2% to 12%)
Not available	2 (2%; 0.3% to 8%)	75 (75%; 65% to 82%)
Type of registration		
Prospective	80 (80%; 71% to 87%)	50 (50%; 40% to 60%)
Retrospective	20 (20%; 13% to 29%)	22 (22%; 15% to 32%)
Unclear	–	28 (28%; 20% to 38%)
Registration of a data-sharing plan		
Yes	10 (10%; 5% to 18%)	8 (8%; 4% to 16%)
Yes, but not in original version	12 (12%; 7% to 20%)	5 (5%; 2% to 12%)
No	78 (78%; 68% to 85%)	87 (87%; 78% to 93%)

ICMJE, International Committee of Medical Journal Editors.

RCTs published in ICMJE-member journals

The results are displayed in table 3 for the 100 selected articles. Among these, 30 were from *NEJM*, 28 from *The Lancet*, 17 from *JAMA*, 13 from *PLOS Medicine*, 5 from the *Annals of Internal Medicine*, 3 from *The BMJ*, 2 from the *Journal of Korean Medical Sciences* and 2 from the *German Medical Journal*.

Almost all the articles (98%; 92% to 99%) had a data-sharing statement. The two articles without data-sharing statements were from the *Journal of Korean Medical Science* and were confirmed as having been submitted after 1 July 2018. Of the statements 67% (57% to 76%) indicated an intention to share data, while the intention was unclear for an additional 10 (10%; 5% to 18%). The characteristics of the data-sharing plans are detailed in table 4.

Of the 77 articles with data-sharing intentions, 7 (9%) mentioned access to other data from the study, besides IPD (eg, data frame for 'unpublished data'/'medical coding dataset'/'non-patient-level data'). Of the 77 articles, 63 (82%) mentioned sharing for the following supplementary documents: study protocol (for 51), statistical analysis plan (for 37), informed consent form (for 15), data dictionary (for 14) and case report form (for 5). Time restriction for IPD was present in 34 of 77 (44%) data sets for either the start date of data-sharing, the end date or both. In two data-sharing statements, it was clear that data were to be available directly after approval of the drug in the European Union and in the USA. In 28 out of 30 other cases there was an embargo: 8 after 2 years, 2 after 18 months, 15 after 1 year, 1 after 9 months, and 2 after 3 months. A restricted access period was specified for 12 data sets: six of these specified restricted access for 2 years, three for 1 year, one for 5 years, one for 10 years, and for one it was stated that the time would be defined by the committee. Of 77 data-sharing statements, 60 (78%) specified that data could only be used for specific reasons: 53 mentioned a scientific aim only, 6 indicated willingness to share data specifically for meta-analyses or individual meta-analyses, and 1 data-sharing statement specified that the aim of the reuse was to be focused on a particular disease (herpes zoster). A specific mechanism was detailed in 68 of 77 (88%) data-sharing statements. Thirty-five only mentioned the need to establish a data-sharing agreement and/or a formal data request, 20 indicated that an email contact was necessary, and 13 mentioned data-sharing platforms.

Twenty-two of 100 (22%) had registered a data-sharing plan on registers such as ClinicalTrials.gov. Of these, 14 specified IPD data-sharing, 6 did not, and for 2 it was unclear.

RCTs published in ICMJE-affiliated journals

The 100 selected RCTs were from 38 different journals (mean number of RCTs per journal=11 (±10)). We found 25 RCTs with data-sharing statements. Seventeen authors/teams (17%; 10% to 26%) declared an intention to share, while the intention was unclear for an additional five (5%; 2% to 12%). The characteristics of the data-sharing plans are detailed in tables 3 and 4. Seven of 22 (32%) articles with a positive (or unclear) intention to share data expressed in a data-sharing statement indicated that other data sets, besides IPD, would be available. Regarding the sharing of any other documents, authors stated they would share study protocols (for seven studies), the statistical analysis plan and the study report (for four studies), and the case report form (for

Table 4 Characteristics of the data-sharing statements for articles with an intention to share individual patient data (including those with unclear intentions)

	Articles in ICMJE-member journals (n=77)	Articles in ICMJE-affiliated journals (n=22)
Intention to share code		
Yes	9 (12%; 6% to 22%)	0
No	17 (22%; 14% to 33%)	0
Unclear	51 (66%; 54% to 76%)	22 (100%)
Intention to share other research data		
Yes	6 (8%; 3% to 17%)	7 (32%; 15% to 55%)
No	14 (18%; 11% to 29%)	0
Unclear	57 (74%; 63% to 84%)	15 (68%; 45% to 85%)
Intention to share any other documents		
Yes	63 (82%; 71% to 89%)	10 (46%; 25% to 67%)
No	1 (1%; 0.1% to 8%)	0
Unclear	13 (17%; 10% to 28%)	12 (54%; 33% to 75%)
Restriction of time for availability		
Yes	34 (44%; 33% to 56%)	10 (46%; 25% to 67%)
No	22 (29%; 19% to 40%)	8 (36%; 18% to 59%)
Unclear	21 (27%; 18% to 39%)	4 (18%; 6% to 41%)
Free access		
Yes	7 (9%; 4% to 18%)	1 (4%; 0.2% to 25%)
No	69 (90%; 80% to 95%)	21 (96%; 75% to 99%)
Unclear	1 (1%; 0.1% to 8%)	0
Possibility to use data for any type of purpose		
Yes	7 (9%; 4% to 18%)	1 (4%; 0.2% to 25%)
No	60 (78%; 67% to 86%)	14 (64%; 41% to 82%)
Unclear	10 (13%; 7% to 23%)	7 (32%; 15% to 55%)
Specific kind of access mechanism		
Yes	68 (88%; 78% to 94%)	21 (96%; 75% to 99%)
No	7 (9%; 4% to 18%)	1 (4%; 0.2% to 25%)
Unclear	2 (3%; 0.5% to 10%)	0
Reviewed by a committee that is independent of the sponsor/author?		
Yes	18 (23%; 15% to 35%)	4 (18%; 6% to 41%)
No	22 (29%; 19% to 40%)	0
Unclear	37 (48%; 37% to 60%)	18 (82%; 59% to 94%)

ICMJE, International Committee of Medical Journal Editors.

two studies). Time restriction was present for 10 out of 22 (46%) data sets. Three data sets had a limitation for the start date of data-sharing, ranging from 12 months to 18 months and up to 3 years. For the end date of data availability, the following time frames were collected: 5 years in two cases, 3 years for one, 2 years for one, 1 year for three and 3 months for one. For the question as to whether data could be used for any type of purpose, 14 out of 22 (64%) eligible data sets were only available for specific purposes (ie, research). For 10 of these cases the scientific aim was mentioned but not detailed, and in four statements no aim was specified at all. A specific kind of access mechanism was cited in 21 of 22 (96%) statements. Six of them mentioned a data-sharing agreement, one referred to a data platform, and fourteen data sets could be requested by email. For the 13 out of 100 (13%) trials with registration of their data-sharing plan, 2 planned to share the data, 6 did not, and for 5 it was unclear.

DISCUSSION

Statement of principal findings

In our survey we found that 57% of ICMJE-member journals had an explicit data-sharing policy on their website and that approximately a third of the ICMJE-affiliated journals had one. Slightly more than a third

of the member journals and most of the affiliated journals (around 56%) referred to the ICMJE guidelines without specifying a specific data-sharing policy. In addition, nearly 60% of the affiliated journals with an explicit policy had a less demanding policy than that required by the ICMJE. In contrast, the former ICMJE policy of trial registration was better implemented, with more than 71% of member journals and 66% of the affiliated journals explicitly requiring it as part of their policies.

For journals with a data-sharing policy, a data-sharing statement was frequent among member journals (98%), with rates of intention to share data of around 77%. These rates are in line with the intention to share previously reported in the *Annals of Internal Medicine*.[14] In contrast, among ICMJE-affiliated journals with a data-sharing policy, data-sharing statements were not frequent (25%), and the intention to share data was only found in 22% of RCTs published in journals with an explicit data-sharing policy. Importantly, the statements often refer to data-sharing on request, and rarely to a specific repository or to fully available data sets. We already know that, even under a strict data-sharing policy such as the policy in place at *The BMJ* and *PLOS Medicine*, data availability is suboptimal, even when researchers express an intention to share.[15] And indeed, in a recent scoping review[16] we found that while the willingness to share data was generally high across trials, actual data-sharing rates were generally lower. In addition, there was considerable heterogeneity in data-sharing statements, with a focus on IPD data, and with very inconsistent information related to statistical codes and other documents (eg, the study protocol or the study report), which are key elements for reproducible research.[17] Our results therefore question whether the new ICMJE policy as implemented by journals adequately supports clinical trial data-sharing, and they underline the need for efforts towards more reproducible research. Although data-sharing is only one aspect among others (eg, registration/best practices in reporting), without data-sharing, reproducibility is not possible.

Few characteristics were found to be associated with an explicit data-sharing policy. All were related to the publishers and the World Bank wealth category of the country/region of the editorial offices. As observed in previous research,[18] a positive association between the JIF and data-sharing was found in univariate analysis, but it did not survive in the multivariate analysis. While the JIF is often (incorrectly) thought to be a surrogate for journal quality, our study suggests that professionalism and characteristics of the publisher and the editorial office resources could be better markers of quality and the implementation of reproducible research policies.

Findings in relation to other studies

A similar survey conducted in 2019 by our team also identified lack of implementation of basic data-sharing instructions in surgery journals with a JIF over 2. Only 50% of the journals had a data-sharing policy on their website,[19] and in general these policies were not as demanding as those required by the ICMJE.

Furthermore, research done by Dal-Ré and Marušić[20] found independently an alike number of predatory journals in the list of journals which claim to follow the ICMJE recommendations.

It is important to note here that almost all the 'big' publishing houses have different data-sharing policies for their different journals (eg, the BMJ Group has three levels of data-sharing policy, and Taylor & Francis have five different types).[21 22] A related analysis was conducted by Mellor[23] on the various data-sharing policies of the four big publishing houses, Elsevier, Springer Nature, Taylor & Francis and Wiley. This survey compared the Transparency and Openness (TOP) guidelines with the data-sharing policies of the different journals.[24] Similar definitions to the ones we used to define more or less stringent requirements were adopted, and the authors found that most of the basic or level 1 data-sharing policies were not even TOP-compliant. This confirms our impression that even if policies are in place, they are not sufficiently demanding to be liable to change the data-sharing culture. A harmonisation needs to be established, and previous successful experiences should be taken into account.[25 26]

Limitations of this study

In our study, we had to rely on online information, as it proved difficult to contact editors and ascertain the existence of data-sharing policies. While all included journals had an electronic format, we cannot exclude that some may have implemented a policy without mentioning its enforcement explicitly on its website. In addition, we are studying a moving target in a changing environment, and it is likely that some journals that had no explicit policy when we performed our search have now implemented one. Repeated monitoring of the implementation of data-sharing policies therefore seems necessary. Another limitation was that we did not check specifically whether the data sets were actually made available when the authors indicated availability in the statement, nor did we request any data to ascertain data availability. Data availability rates could indeed be lower than suggested in an intention to share, as observed in *The BMJ* overall,[27] and more particularly for clinical trial data, even after communicating with the study authors.[15] Moreover, it would be interesting to see how many funders or academic institutions really share their data after expiry of the time restrictions indicated.

A further limitation was the language filter. Due to lack of resources we were not able to include every language. This might have caused bias, as for instance Russian journals might have presented a different data-sharing policy from journals that publish in English.

A large range of journals were included, especially in terms of quality. We tried to limit the inclusion of 'predatory journals' using Beall's list. In this matter there is no real gold standard, as no exact definition existed when we

planned our study. Other lists such as Cabell's blacklist show an overlap with Beall's list.[28] Recently, a new definition has been proposed[29] and it could help to better identify predatory journals. On the one hand, we were surprised by the large number of ICMJE-affiliated journals referenced on the ICMJE website and listed in Beall's list. On the other hand, the investigators performing the data extraction had the impression that some of the selected journals had very poor editorial standards (in cases where instructions for authors were not clear and information was not given for all the steps of the editorial process) and could also fit the definition of predatory journals.

Finally, our identification of factors associated with an explicit data-sharing policy is only exploratory. Several unmeasured confounders, for instance the journal's income and/or the numbers of RCTs published by a given journal, could account for some of the associations found. Other unmeasured confounders may exist and great caution is warranted in interpreting these results, which naturally cannot be considered as reflecting any causal relationship.

Perspectives

It appears that data-sharing policies are infrequent and poorly enforced in most ICMJE-affiliated journals. Perhaps the journals do not know how best to implement the policy, or they may be worried they will lose submissions if the policies are implemented. Other explanations could be the costs resulting from the process or the greater labour intensity. It is also possible that some authors, researchers and indeed editors may be opposed to data-sharing policies. In addition, there is no specific enforcement for an affiliated journal to follow the ICMJE guidelines. It can be noted that the ICMJE states on its website that they 'cannot verify the completeness or accuracy of this list' and that 'there may be some listed journals that do not follow all of the many recommendations and policies in the document'.[7] Furthermore, the large proportion of presumed predatory journals we found as well as the small proportion of journals enforcing the new policy are of concern for the impact and credibility of the ICMJE. We suggest that journals provide audits and feedback (to readers), especially as the number of ICMJE-affiliated journals is growing very fast, with 4725 in November 2018[30] and already 5504 in November 2019[7] (+16% in 1 year). Without such checks, journals with poor editorial practices could present affiliation with the committee as an endorsement of a sort of quality label in biomedical journals, while this is not the case. The ICMJE affiliation could be indeed perceived as a guarantee, since these standards have of course been endorsed by more than three-quarters of the most prominent journals in biomedicine, as illustrated by Shamseer and colleagues in 2016.[31]

In addition, continuous audits of journal policies and their enforcement could be used as a better indicator of journal quality than the current exclusive focus on the JIF. There is room for development of new responsible metrics in this area, encompassing other aspects of reproducible research practices, such as registration policies and the use of reporting guidelines.[32] And indeed, data-sharing is only one facet of reproducible research policies.

Steps in the right direction have already been taken, such as the uniform guidelines for data-sharing in journals that have been developed by the Data Policy Standardisation and Implementation Interest Group of the Research Data Alliance.[33] This could help to reach the goal of full transparency and data-sharing for clinical trial results, since the implementation of the current ICMJE policy seems suboptimal.

Correction notice Size of the figure 1 has been increased.

Twitter Maximilian Siebert @ReiTheR_RCT and David Moher @dmoher

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REFERENCES

1 Taichman DB, Sahni P, Pinborg A, *et al*. Data sharing statements for clinical trials: a requirement of the International Committee of medical Journal editors. *Ann Intern Med* 2017;167:63–5.
2 Laine C, Goodman SN, Griswold ME, *et al*. Reproducible research: moving toward research the public can really trust. *Ann Intern Med* 2007;146:450–3.
3 Groves T. Managing UK research data for future use. *BMJ* 2009;338:b1525
4 Godlee F, Groves T. The new BMJ policy on sharing data from drug and device trials. *BMJ* 2012;345:e7888.
5 Loder E, Groves T. The BMJ requires data sharing on Request for all trials. *BMJ* 2015;350:h2373.
6 Bloom T, Ganley E, Winker M. Data access for the open access literature: PLOS's data policy. *PLoS Biol* 2014;12:e1001797.
7 International Committee of Medical Journal Editors. Journals stating that they follow the ICMJE Recommendations, 2019. Available: http://www.icmje.org/journals-following-the-icmje-recommendations/ [Accessed 9 Dec 2019].
8 Beall J. Beall's list of predatory journals and publishers, 2020. Available: https://beallslist.weebly.com/ [Accessed 15 Jan 2020].

9 R Core Team. *R: a language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing, 2018.
10 Open Science Framework. Maximilian Siebert, 2020. Available: https://osf.io/b5nq7/
11 The World Bank. World bank country and lending groups, 2020. Available: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups [Accessed 28 Jan 2020].
12 Lefebvre C, Manheimer E, Glanville J. Searching for studies. In: *Cochrane Handbook for systematic reviews of interventions*. The Cochrane Collaboration, 2011. www.training.cochrane.org/handbook
13 Kosmidis I. *brglm: bias reduction in Binary-Response generalized linear models*. R package version 0.6.2 ED, 2019. https://cran.r-project.org/package=brglm
14 Laine C, Berkwits M, Mulrow C, *et al*. *Reproducible research: biomedical researchers' willingness to share information to enable others to reproduce their results*. Vancouver: International Congress on Peer Review and Scientific Publication, 2009.
15 Naudet F, Sakarovitch C, Janiaud P, *et al*. Data sharing and reanalysis of randomized controlled trials in leading biomedical journals with a full data sharing policy: survey of studies published in *The BMJ* and *PLOS Medicine*. *BMJ* 2018;360:k400.
16 Ohmann C, Moher D, Siebert M, *et al*. *Status, use and impact of sharing individual participant data from clinical trials: a scoping review*, 2019.
17 Munafò MR, Nosek BA, Bishop DVM, *et al*. A manifesto for reproducible science. *Nat Hum Behav* 2017;1.
18 Vasilevsky NA, Minnier J, Haendel MA, *et al*. Reproducible and reusable research: are Journal data sharing policies meeting the mark? *PeerJ* 2017;5:e3208.
19 Lombard N, Gasmi A, Sulpice L. Research transparency promotion by surgical journals publishing randomised controlled trials: a survey. *medRxiv* 2019:19002386.
20 Dal-Ré R, Marušić A. Potential predatory journals are colonizing the ICMJE recommendations list of followers. *Neth J Med* 2019;77:92–6.
21 BMJ Author Hub. Data sharing, 2018. Available: https://authors.bmj.com/policies/data-sharing/ [Accessed 24 Mar 2020].
22 Author Services. Understanding our data sharing policies, 2020. Available: https://authorservices.taylorandfrancis.com/data-sharing-policies/ [Accessed 24 Mar 2020].
23 Mellor D. The landscape of open data policies, 2018. Available: https://cos.io/blog/landscape-open-data-policies/
24 Nosek BA, Alter G, Banks GC, *et al*. Promoting an open research culture. *Science* 2015;348:1422–5.
25 Hardwicke TE, Mathur MB, MacDonald K, *et al*. Data availability, reusability, and analytic reproducibility: evaluating the impact of a mandatory open data policy at the journal *Cognition*. *R Soc Open Sci* 2018;5:180448.
26 Giofrè D, Cumming G, Fresc L, *et al*. The influence of Journal submission guidelines on authors' reporting of statistics and use of open research practices. *PLoS One* 2017;12:e0175583.
27 Rowhani-Farid A, Barnett AG. Has open data arrived at the British medical Journal (BMJ)? an observational study. *BMJ Open* 2016;6:e011784.
28 Strinzel M, Severin A, Milzow K, *et al*. Blacklists and Whitelists to tackle predatory publishing: a cross-sectional comparison and thematic analysis. *MBio* 2019;10:mBio.00411-19.
29 Grudniewicz A, Moher D, Cobey KD, *et al*. Predatory journals: no definition, no defence. *Nature* 2019;576:210–2.
30 International Committee of Medical Journal Editors. Journals stating that they follow the ICMJE recommendations, 2018. Available: http://www.icmje.org/journals-following-the-icmje-recommendations/ [Accessed 9 Dec 2019].
31 Shamseer L, Hopewell S, Altman DG, *et al*. Update on the endorsement of CONSORT by high impact factor journals: a survey of journal "Instructions to Authors" in 2014. *Trials* 2016;17:301.
32 Moher D, Naudet F, Cristea IA, *et al*. Assessing scientists for hiring, promotion, and tenure. *PLoS Biol* 2018;16:e2004089.
33 Hrynaszkiewicz I, Simons N, Hussain A. Developing a research data policy framework for all journals and publishers. *Data Sci J* 2019;19:dsj-2020-005.

INTENT TO SHARE ANNALS OF INTERNAL MEDICINE'S TRIAL DATA WAS NOT ASSOCIATED WITH DATA RE-USE

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Highlights / What is new:

- Published re-uses are mainly secondary analyses. Only a few meta-analyses of individual participant data are performed, and no re-analyses were identified.
- Although more than half of the articles mention willingness to share their datasets, no significant association was found between intention-to-share and published re-uses of the data.
- The ICMJE policy needs to implement an evaluation component in its new policy.

ABSTRACT

Objective: To explore the impact of the Annals of Internal Medicine (AIM) data-sharing policy for randomized controlled trials (RCTs) in terms of output from data-sharing (i.e. publications re-using the data).

Study design and setting: Retrospective study. RCTs published in the AIM between 2007 and 2017 were retrieved on PubMed. Publications where the data had been re-used were identified on Web of Science. Searches were performed by two independent reviewers. The primary outcome was any published re-use of the data (re-analysis, secondary analysis, or meta-analysis of individual participant data [MIPD]), where the first, last and corresponding authors were not among the authors of the RCT. Analyses used Cox (primary analysis) models adjusting for RCTs characteristics (registration: https://osf.io/8pj5e/).

Results: 185 RCTs were identified. 106 (57%) mentioned willingness to share data and 79 (43%) did not. 208 secondary analyses, 67 MIPD and no re-analyses were identified. No significant association was found between intent to share and re-use where the first, last and corresponding authors were not among the authors of the primary RCT (adjusted hazard ratio = 1.04 [0.47-2.30]).

Conclusion: Over ten years, RCTs published in AIM expressing an intention to share data were not associated with more extensive re-use of the data.

Keywords: Data sharing, Open science, Clinical Research, Randomized Controlled Trial, Re-use of data, Meta-research

Running title: Intent to share trial data and data re-use

Word Count: 3985

Title: Intent to share Annals of Internal Medicine's trial data was not associated with data re-use

1. INTRODUCTION

Data-sharing (i.e. sharing of data, codes, programs and material) is the norm in many scientific disciplines, but until recently this has not been the case with biomedical research (1). In medicine, randomized controlled trials (RCTs) are considered influential and therefore availability of their data is expected to be crucial in the evaluation of health interventions (e.g. for meta-analyses of individual participant data, MIPD). In June 2017, the International Committee of Medical Journal Editors (ICMJE) required a data-sharing plan to be included in each paper (and pre-specified in study registration) (2). As these new requirements for publishing experimental findings come into effect, it is necessary to assess whether they have their intended effects.

Among the leading general medical journals, the New England Journal of Medicine (NEJM), The Lancet, the JAMA and JAMA Internal Medicine have had no specific policy for sharing data from RCTs until recently. The British Medical Journal (BMJ) and the Public Library of Science (PLOS) Medicine have already adopted stronger policies, reaching beyond the ICMJE policy, which render data-sharing mandatory with the publication of RCTs. Nevertheless, in view of actual data-sharing rates their policy seems imperfect (3).

The Annals of Internal Medicine (AIM) has encouraged (but not required) data-sharing since 2007 (4). Since then, the journal has required a reproducible research statement to be included in every original research article (including RCTs). This reproducible research statement indicates "whether the study protocol, data, or statistical code is available to readers, and under what terms authors will share this information." While this policy did not make data-sharing mandatory, its aim was "to help the scientific community evaluate, and build upon, the research findings" published in AIM. Importantly, this is to a large extent what is required by the new ICMJE policy. Therefore, a retrospective analysis of RCTs published in AIM between 2007 and 2017 could provide a proxy for the expected impact of the ICMJE policy.

We explored the effectiveness of RCT data-sharing from AIM publications in terms of output from data-sharing (i.e. publications where the data has been re-used). We specifically aimed to describe the data-sharing practices in RCTs published in AIM over a decade (2007-2017), to assess the association between intent to share and published re-uses of data, and to assess the association of intent to share with citation rates.

2. METHODS

The methods were specified in advance. They were documented in a protocol registered with the Open Science Framework (OSF) on 3rd August 2018 (https://osf.io/gnt6u/).

2.1. ELIGIBILITY CRITERIA

We surveyed a retrospective cohort of RCTs published in the AIM between April 2007 and December 2017. The RCTs included the following designs: two parallel groups and multiple groups, cluster trials and cross-over studies, non-inferiority and superiority trials. All publications were inspected to exclude secondary analyses and re-analyses of a previously published RCT. Publications without reproducible research statements (i.e. those that did not comply with the policy) were excluded.

2.2. SEARCH STRATEGY AND SELECTION OF PRIMARY PUBLICATIONS OF STUDIES IN AIM

We identified eligible studies from PubMed/Medline using the following strategy: (annals of internal medicine) AND ("2007/04/01"[Date - Publication]: "2017/12/31"[Date - Publication]) / limitation randomized controlled trial.

Two reviewers (CP and AJLB) performed the eligibility assessment independently. Disagreements were resolved by consensus or in consultation with a third reviewer (FN).

2.3. SEARCH STRATEGY AND STUDY SELECTION FOR PUBLISHED RE-USES

We used the Clarivate Web of Science database to identify secondary publications derived from these primary trials, since it would be extremely unlikely for a secondary publication not to cite the primary trial. We identified and recorded the total number of citations for each primary publication. We recorded the number of citations by articles that used individual patient data from the primary article in the Annals. For articles considered as potentially secondary publications, the abstracts and, when necessary, full texts were examined by two independent reviewers (among LC, JG, and MV) to confirm eligibility. One reviewer inspected all included citations and when he disagreed with the inclusion, disagreements were resolved in consultation with a third reviewer (FN). In addition, whenever a methodological article was cited in the primary article in the Annals (i.e. an article describing the methods and protocol of a trial), we entered this article in the Web of Science searches to identify additional citations.

2.4. DATA EXTRACTION

A data extraction sheet was developed. For each article included, we extracted information on study characteristics (date of publication, country (USA/Europe/Asia/other), intervention type (drug/device/complex intervention), control group (active/inactive), medical specialty (medicine/surgery/psychiatry), total sample size, result on the primary outcome (positive/negative), and funding source (academic/industry/charity/mixed). Detailed information on the data-sharing plan was extracted from the reproducible research statement. We recorded whether a statement indicated that the data was available (i.e. intent to share data). If the authors intended to share data, we extracted the type of data-sharing plan (1/ directly available, 2/ available upon request) and the type of material that was intended to be shared (1/ data-set, 2/ code, 3/ study protocol). We relied on information declared by the authors in the "reproducible research statement". In case of study protocols, intention to share by authors can include full text protocols and/or protocols available only in registries. If the authors did not intend to share data, we extracted reasons for not sharing data (when available).

Two authors (CP and AJLB) independently extracted the data from the studies included. Disagreements were resolved by consensus or in consultation with a third reviewer (FN).

2.5. OUTCOMES

Our primary outcome was the re-use of data (yes/no) documented in all the citing articles on Web of Science. This is a composite outcome defined by any secondary use 1/ in a re-analysis, 2/ in a secondary analysis and 3/ in a MIPD (we used a broad definition including both systematic reviews with MIPD and pooled analyses without systematic review). The primary outcome was limited to published re-uses where the first, last and corresponding authors were not among the authors of the primary article in the Annals.

The pre-specified secondary outcomes were as follows: 1/ Components (1, 2, and 3) of the primary outcome; 2/ Re-use of the data (yes/no) documented in all the citing articles, on Web of Science without the author restriction used for the primary outcome; 3/ Number and type of secondary use (re-analyses, secondary analyses, MIPD) in which the lead authors (first, corresponding and last) of the published re-use of the data were outside the team authoring the primary article in the Annals; 4/ Number and type of secondary use (re-analyses, secondary analyses, MIPD) by an independent team (no author in common); 5/ Number and type of secondary use (re-analyses, secondary analyses, MIPD) by a team where <50% of authors were among the authors of the primary article in the Annals; 6/ Number and type of secondary use (re-analyses, secondary analyses, MIPD) by a team

where ≥50% of authors were among the authors of the primary article in the Annals; 7/ Number and type of secondary use (re-analyses, secondary analyses, MIPD) by a team where 100% of authors were among the authors of the primary article in the Annals; 8/ Mention in the published re-uses of the availability of the data re-used (yes/no) and how it was used (qualitative data); 9/ Number of citations (on Web of Science).

2.6. STATISTICAL ANALYSIS

A detailed statistical analysis plan was registered with the OSF on 1st August 2019 (https://osf.io/zck9y/) prior to merging the AIM primary articles database and the re-use database. The general strategy for modeling was as follows: we first used a univariate model with fixed effects to explore solely the relationship between the dependent and the explanatory variables, adjusting on possible confounders (country, intervention type, control group, medical specialty, result (positive/negative) on the primary outcome, funding source, and sample size). All associations with a p-value <0.25 were subsequently explored in a multivariate model. In all final models, we considered adding a random effect to account for studies that were published by the same team (defined as groups of primary AIM articles clustered by any common authors).

We described 'intent to share data' rates over time using a logistic regression (model diagnostics checked for linearity, multicollinearity and absence of influential observations). Results are expressed as odds ratios (OR) with their 95% confidence intervals (CIs). The primary outcome and all its components were analyzed using Kaplan-Meier test and compared using proportional hazards regression (model diagnostics checked for linearity, proportional hazards and absence of influential observations). Results are expressed as hazard ratios (HR) with their 95% CI. Other secondary outcomes were analyzed as count data using Poisson or (when necessary) binomial negative regressions (model diagnostics checked for linearity and absence of overdispersion). Results are expressed as incidence rate ratios (IRR) with their 95% CI. Model diagnostics are detailed in the statistical analysis plan and their results can be accessed on the OSF (https://osf.io/8pj5e/).

All statistical analyses were performed at a 5% significance level (two-sided tests). All analyses were performed under R version 3.4.1 (2017-06-30, The R Foundation for Statistical Computing).

2.7. CHANGES FROM THE INITIAL PROTOCOL

The following clarifications were described prior to the analyses in the statistical analysis plan: 1/ we decided to classify pooled analyses as MIPD because this point was unclear in the initial

protocol, 2/ we made it clear that the year of publication (and date) was used to calculate each follow-up time (date of publication to date of citation searches) in survival models and as an offset in count models, and not as a potential confounder and 3/ also, we excluded citations concerning long-term follow-up and use of stored biological samples, since these analyses obviously implied the acquisition of new data.

We considered the sample size of the primary article in the Annals as a potential confounder, since it could be responsible for changes in both the intent to share and the number of re-uses, and therefore could be an important confounding factor, which we omitted to plan for in our initial protocol.

While we initially planned to include 3 types of re-use (secondary analyses, re-analyses and MIPD), we decided to include meta-analyses of aggregate data as supplementary analyses. Indeed, data availability can have an impact when the initial publication does not report the data required to perform the meta-analysis.

2.8. Role of the funding source

This work was supported by the Fondation pour la Recherche Médicale, grant number 6616 to Claude Pellen, and Région Bretagne Boost ERC grant (18HC432-01N). Work by FN on data-sharing is supported by a grant from the French National Research Agency – ANR (Reproducibility in Therapeutic Research / ReITheR: ANR-17-CE36-0010-01). The funders were not involved in the study design, data collection, analysis, interpretation, or writing of the manuscript.

3. RESULTS

3.1. Characteristics of primary articles and published re-uses

Figure 1 shows the study selection process. The searches carried out on 27th May 2018 retrieved 257 items. Of these, 185 were primary articles and had a data-sharing statement; these articles were included. These RCTs had a median sample size of 299 participants (interquartile range (IQR) [158-719]), they had academic funding in 79 cases (42.7%), and were led by teams from USA in 97 cases (52.4%). Eighty-eight RCTs (47.6%) evaluated drug interventions, 89 (48.1%) complex interventions (e.g. psychotherapeutic program), and 8 (4.3 %) evaluated devices. Based on the data-sharing statements in the articles, 106 studies mentioned willingness to share the dataset and 79 mentioned that the data were not available. Of these, none provided a reason for not sharing. **Table 1** presents the characteristics of these studies displayed by intent to share or not.

Search for re-uses of these primary articles were carried out on 9th August 2018. There were 15,378 citations identified through Web of Science searches (14,576 from primary articles and 802 more from protocols of these studies). Among these, we identified 208 secondary analyses, 67 MIPD, and 0 re-analyses. We also identified 407 meta-analyses of aggregate data.

3.2. INTENT TO SHARE TRENDS OVER TIME

Figure 2 shows data-sharing trends over time. We found no association between 'intent to share data' rates and time (years) (OR = 1.00 [0.90 -1.11], adjusted OR = 0.98 [0.84-1.13]). Details of the adjusted model are provided in **Web-appendix 1**. Proportions of code and protocol availability were always higher than levels of intent to share data, and reached 100 % for protocol availability in 2017.

3.3. ASSOCIATION BETWEEN INTENT TO SHARE AND PUBLISHED RE-USES OF DATA

Over 10 years, 185 trials were available. Among the 106 of them mentioning willingness to share the dataset, 14 (13.2%) had at least one published re-use where the first, last and corresponding authors were not among the authors of the original RCT. Among the 79 others, 12 (15.2%) had at least one published re-use where the first, last and corresponding authors were not among the authors of the original RCT.

Univariate and multivariate analyses (**Figure 3**) identified no significant association between intent to share and the primary outcome, that is to say published re-uses of the data where the first, last and corresponding authors were not among the authors of the primary article in the Annals (adjusted HR = 1.04 [0.47-2.30]), nor was there any association with its different components (adjusted HR = 0.96 [0.32-2.90] for secondary analyses, adjusted HR = 1.23 [0.37-4.06] for MIPD). The same results were observed in analyses using no author restriction criteria (adjusted HR = 1.30 [0.84-2.01]). Supplementary analyses, including meta-analyses of aggregate data not specified in the registered protocol, are presented in **Web-appendix 2**. The results were consistent with those of the main analysis.

Figure 4 presents count outcomes related to the number of re-uses (by different types of re-use). A few statistically significant associations were found in univariate analyses but they were not confirmed in multivariate analyses for pre-specified outcomes. Only the outcome "MIPD/pooled analyses with no author in common with the primary RCT" retained a weak association signal in multivariate analyses. The number tended to be greater when there was no mention of data-sharing

(adjusted IRR = 0.03 [0.00-0.33]). A careful examination of individual papers found that among the 13 re-uses of RCTs stating they have no intention to share, 12 had the same funder as the primary RCTs, all of these being sponsored by pharmaceutical firms (**Web-appendix 3**). These results are presented in detail in **Web-appendix 4**, and the number of re-uses per RCT are presented in **Web-appendix 5**.

3.4. Association between intent to share and number of citations

Univariate and multivariate analyses identified no significant association between intent to share and the number of citations, with 134 citations per 10 publication-years for papers with an intention to share statement and 149 per 10 publication-years for papers stating they had no intention to share (IRR = 0.83 [0.67-1.02]; adjusted IRR = 0.90 [0.72-1.13]).

4. DISCUSSION

4.1. Statement of primary findings

Over ten years, one might have expected a progressive increase in data-sharing practices with a progressive improvement in data-sharing intent over time. However, and in line with a previous exploration of intent to share data for all research articles in AIM between 2008 and 2012 (5), we did not find any such increase. Interestingly, while Laine et al. (6) found that the intention to share protocols was lower than for the intention to share datasets, we found the opposite, with higher, increasing rates of intention to share protocols, reaching 100% in 2017. This result could be explained by our specific focus on clinical trials. Protocol availability is a core feature of transparency for these studies, especially in the context of the strong, justified external pressure by some watchdog groups. For instance, in response to the efforts by the Centre for Evidence-Based Medicine Outcome Monitoring Project (COMPare) (7) to document outcome switching in RCTs, the Annals editor recalled that the journal routinely asks authors of clinical trials to submit their protocols with their manuscripts, and examines trial registries for the initial and final information entered about trials (8). In data-sharing statements, intention to share codes was always more prominent than the sharing of data. This result is curious, since codes without the data are most often useless.

While more than 55% of the primary articles surveyed intended to make their data available, no association was found between intent to share and re-use of the data. Interestingly, there were only a few published re-uses of the primary articles, and three-quarters were secondary analyses. MIPD were the remaining re-uses and we found no re-analyses, meaning that none of the re-uses of the data was for reproducibility purposes. This last result is unfortunate given the increased deployment of reproducibility checks in other fields (9). However, this observation is in line with an earlier survey

(10) exploring requests for data access from the National Heart, Lung and Blood Institute data repository. Over 16 years, 100 trials were available, 88 of them had a data request and 47 had at least one publication resulting from data-sharing. More than 80% of requests were for secondary analyses or methodological developments, and only 7% were for MIPD. In this survey, only two requests concerned re-analyses. And indeed, there is almost no culture of performing and publishing re-analyses in the clinical trial literature (11), especially by entirely independent authors. Perhaps fear of "hostile" re-analyses or even the possibility that any re-analyses are liable to obtain different results could explain lack of data sharing for this specific purpose. Another survey of cardiometabolic clinical trials available on the clinical study data request platform (12) suggested that despite efforts to make data available, re-uses were rare. Over 4 years, only 3 re-uses had been published among the 537 studies available for access. Similarly, over 11 years (13), only 14 re-uses (5 secondary analyses and 9 MIPD) were published using 51 clinical trial datasets available on the Data Share platform of the National Institute on Drug Abuse. Altogether, these results suggest that, despite some important efforts, data-sharing policies does not systematically achieve large numbers of published outputs.

Different factors could explain this finding. First, the available datasets may not be requested (and used) by external researchers. Second, primary authors may refuse to share their data as promised in their data-sharing statement. For instance, in our survey, only one publication had its dataset directly available on a repository, while all the others were available upon request. Similar rates were observed in a survey (6) of the Annals' first year of the reproducible research statement policy, and in a second survey (5) accounting for articles from 2008 to 2012. When data is available upon request, data retrieval could be suboptimal as suggested by a previous survey of studies published in PLOS Medicine or BMJ under a strict data-sharing policy (3). However, among 90 authors of trials published between January 1, 2012 and March 1, 2016 in PLOS Medicine, The BMJ and the Annals (14), half of the respondents had a data-sharing plan (n = 49) and about one third reported they had received at least one data-sharing request, and very few of these were reported as being refused. It is therefore possible that data is in fact shared, but that re-use of this data will not translate into published output. A cross-sectional web-based survey (15) of the NIH central database repository found that only 67% of the re-uses were published. In addition, shared datasets could serve for pedagogical purpose or for designing trials (e.g. sample size calculation) or any other activity that may not necessarily lead to any published output. However, it is also possible that data-sharing enables numerous secondary analyses to be run, among which only a few reach published posterity. This last hypothesis is of concern, because sub-optimal reporting and selective publication of these re-uses could lead to non-reproducible research (16). In future research, qualitative interviews, including interviews with academic researchers, industry researchers and re-users, could add a finer-grained understanding of these issues.

4.2. LIMITATIONS

Our results should be interpreted cautiously. The observational design of the study does not enable us to draw causal inferences between intent to share and research outputs from actual re-use of data. Confounding is a major issue in observational research, and there is no perfect way to handle it. Despite the adjustment of the analyses to various available factors that might influence the patterns of re-use, some factors could not be fully accounted for. For instance, we were not able to adjust for subtle variations that can arise across different medical subspecialties or topics. Of course, "hot and/or controversial topics" (e.g. vaccines and autism, saturated fat and heart disease) can be associated with both intent to share and re-use, but there is no consensual way to measure this parameter. Also, we did not identify the corresponding author's gender or career stage, while a junior investigator could be more aware of open science practices such as data-sharing. Therefore, this study is prone to residual confounding. In our study, the identification of published re-uses proved to be a difficult task, with the risk of missing some studies. We minimized this risk by using a dual, independent extraction.

Also, it was difficult to define independent re-uses objectively. For instance, the primary article authors could require to be among authors of the re-use as part of their data-sharing statement, even if they were not actively involved in the re-use. This could have introduced some classification bias in our study. For instance, the only signal we identified was for IPD meta-analyses (or pooled analyses) with no author in common with the primary RCT, which were more frequently RCTs without intention to share data. The topics of these RCTs were long-term efficacy of dapagliflozin for patients with diabetes mellitus, adalimumab in moderate to severe Hidradenitis suppurativa, tofacitinib in associations for patients with active rheumatoid arthritis, varenicline in smoking cessation, and the Grazoprevir-Elbasvir combination in Chronic Hepatitis C Virus. The RCT that shared their data was an equivalence trial among treatment-naive volunteers infected with HIV-1. All but one of these re-uses were sponsored by the same funder as the original trial. It is therefore likely that a given funder decided not to release the data and to perform their own research agenda, including series of pooled analyses. Also, classification bias could be differential between studies stating they do or do not intent to share data. For this reason, we used a restriction on the lead authors (first, last and corresponding) for our primary outcome, and performed a series of sensitivity analyses with various definitions. Importantly, all these analyses yielded very similar results.

Most importantly, this retrospective study explores an early experience of data-sharing. The primary articles included in our study cover 10 years during which the AIM pioneered clinical data-sharing, with a few other journals. As a result, re-uses like MIPD needing more than only one study dataset could have been hard to perform, because the overall environment was unfavorable. Up to

2015 most MIPDs were incomplete, half retrieved less than 80% of the eligible individual participant data and retrieval rates across published MIPDs did not improve through these years (17). Improved access to data of a single study may be of limited interest in this environment. Therefore, the generalization of the results obtained from 2007 to 2017 from a single journal to all journals implementing the new ICMJE policy at present under way should be very cautious, as we are operating in a fast-changing landscape.

5. CONCLUSION

Data-sharing policies are coming progressively into effect, and are intended to reform the way clinical research is performed by moving toward a global research community in which sharing deidentified data becomes the norm (18). Our analysis of one of the earliest experiences in the Annals suggests that things are not that simple. While it is hard to extrapolate these findings directly to the new ICMJE policy, our results highlight the need to assess whether this new policy will achieve its intended effects. In our opinion, the ICMJE policy should be assessed in terms of impact with a dedicated evaluation component, which is currently lacking in the formulation of the policy.

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author statement

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6. REFERENCES

1. Iqbal SA, Wallach JD, Khoury MJ, Schully SD, Ioannidis JPA. Reproducible Research Practices and Transparency across the Biomedical Literature. Vaux DL, editor. PLOS Biology. 2016 Jan 4;14(1):e1002333.

2. Taichman DB, Sahni P, Pinborg A, Peiperl L, Laine C, James A, et al. Data sharing statements for clinical trials. BMJ. 2017 Jun 5;j2372.

3. Naudet F, Sakarovitch C, Janiaud P, Cristea I, Fanelli D, Moher D, et al. Data sharing and reanalysis of randomized controlled trials in leading biomedical journals with a full data sharing policy: survey of studies published in *The BMJ* and *PLOS Medicine*. BMJ. 2018 Feb 13;k400.

4. Laine C, Goodman SN, Griswold ME, Sox HC. Reproducible Research: Moving toward Research the Public Can Really Trust. Ann Intern Med. 2007 Mar 20;146(6):450.

5. Griswold M, Laine C, Mulrow C, Schaeffer MB, Stack C. Reproducible Research: Biomedical Researchers' Willingness to Share Information to Enable Others to Reproduce Their Results. Peer Review Congress; 2013.

6. Laine C, Berkwits M, Mulrow C, Schaeffer MB, Griswold M, Goodman S. Reproducible Research: Biomedical Researchers' Willingness to Share Information to Enable Others to Reproduce Their Results. Peer Review Congress; 2009.

7. Goldacre B, Drysdale H, Dale A, Milosevic I, Slade E, Hartley P, et al. COMPare: a prospective cohort study correcting and monitoring 58 misreported trials in real time. Trials [Internet]. 2019 Dec [cited 2019 Sep 6];20(1). Available from: https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-019-3173-2

8. The Editors. Discrepancies Between Prespecified and Reported Outcomes. Annals of Internal Medicine. 2016 Mar 1;164(5):374.

9. Nosek BA, Alter G, Banks GC, Borsboom D, Bowman SD, Breckler SJ, et al. Promoting an open research culture. Science. 2015 Jun 26;348(6242):1422–5.

10. Coady SA, Mensah GA, Wagner EL, Goldfarb ME, Hitchcock DM, Giffen CA. Use of the National Heart, Lung, and Blood Institute Data Repository. New England Journal of Medicine. 2017 May 11;376(19):1849–58.

11. Ebrahim S, Sohani ZN, Montoya L, Agarwal A, Thorlund K, Mills EJ, et al. Reanalyses of Randomized Clinical Trial Data. JAMA. 2014 Sep 10;312(10):1024.

12. Vaduganathan M, Nagarur A, Qamar A, Patel RB, Navar AM, Peterson ED, et al. Availability and Use of Shared Data From Cardiometabolic Clinical Trials. Circulation. 2018 Feb 27;137(9):938–47.

13. Huser V, Shmueli-Blumberg D. Data sharing platforms for de-identified data from human clinical trials. Clinical Trials. 2018 Aug;15(4):413–23.

14. Tannenbaum S, Ross JS, Krumholz HM, Desai NR, Ritchie JD, Lehman R, et al. Early Experiences With Journal Data Sharing Policies: A Survey of Published Clinical Trial Investigators. Annals of Internal Medicine. 2018 Oct 16;169(8):586.

15. Ross JS, Ritchie JD, Finn E, Desai NR, Lehman RL, Krumholz HM, et al. Data sharing through an NIH central database repository: a cross-sectional survey of BioLINCC users. BMJ Open. 2016 Sep;6(9):e012769.

16. Munafò MR, Nosek BA, Bishop DVM, Button KS, Chambers CD, Percie du Sert N, et al. A manifesto for reproducible science. Nature Human Behaviour [Internet]. 2017 Jan [cited 2019 Sep 6];1(1). Available from: http://www.nature.com/articles/s41562-016-0021

17. Nevitt SJ, Marson AG, Davie B, Reynolds S, Williams L, Smith CT. Exploring changes over time and characteristics associated with data retrieval across individual participant data meta-analyses: systematic review. BMJ. 2017 Apr 5;357:j1390.

18. Taichman DB, Sahni P, Pinborg A, Peiperl L, Laine C, James A, et al. Data Sharing Statements for Clinical Trials — A Requirement of the International Committee of Medical Journal Editors. N Engl J Med. 2017 Jun 8;376(23):2277–9.

	Overall	No intent to share	Intent to share	p
Number of articles	185	79	106	
Year of publication median [IQR]	2012 [2010, 2015]	2012 [2010, 2014.5]	2012 [2009, 2015]	0.797*
Geographical zones n (%)				0.318†
Asia	13 (7.0)	8 (10.1)	5 (4.7)	
Europe	54 (29.2)	20 (25.3)	34 (32.1)	
Other	21 (11.4)	7 (8.9)	14 (13.2)	
USA	97 (52.4)	44 (55.7)	53 (50.0)	
Intervention type n (%)				0.620†
Complex intervention	89 (48.1)	35 (44.3)	54 (50.9)	
Device	8 (4.3)	3 (3.8)	5 (4.7)	
Drug	88 (47.6)	41 (51.9)	47 (44.3)	
Control group n (%) **Ref: inactive**	140 (75.7)	61 (77.2)	79 (74.5)	0.804‡
Medical specialty n (%) **Ref: surgery**	4 (2.2)	3 (3.8)	1 (0.9)	0.314†
Primary outcome n (%) **Ref: positive**	123 (66.5)	58 (73.4)	65 (61.3)	0.117‡
Funding source n (%)				0.200†
Academic	79 (42.7)	31 (39.2)	48 (45.3)	
Charity	10 (5.4)	3 (3.8)	7 (6.6)	
Industry	28 (15.1)	17 (21.5)	11 (10.4)	
Mixed	68 (36.8)	28 (35.4)	40 (37.7)	
Sample size median [IQR]	299 [158, 719]	267 [151, 663]	310 [170.25, 722.75]	0.442*
Protocol shared n (%) **Ref: yes**	151 (81.6)	51 (64.6)	100 (94.3)	<0.001‡
Code shared n (%) **Ref: yes**	134 (72.4)	43 (54.4)	91 (85.8)	<0.001‡
Number of citations median [IQR]	59 [29, 114]	71 [36, 116.5]	51.5 [25, 112.75]	0.082*

Table 1. Characteristics of the randomized controlled trials included

*: *Kruskal-Wallis test*
†: *Fisher exact test*
‡: *Pearson's Chi-squared test*

Figures

Figure 1

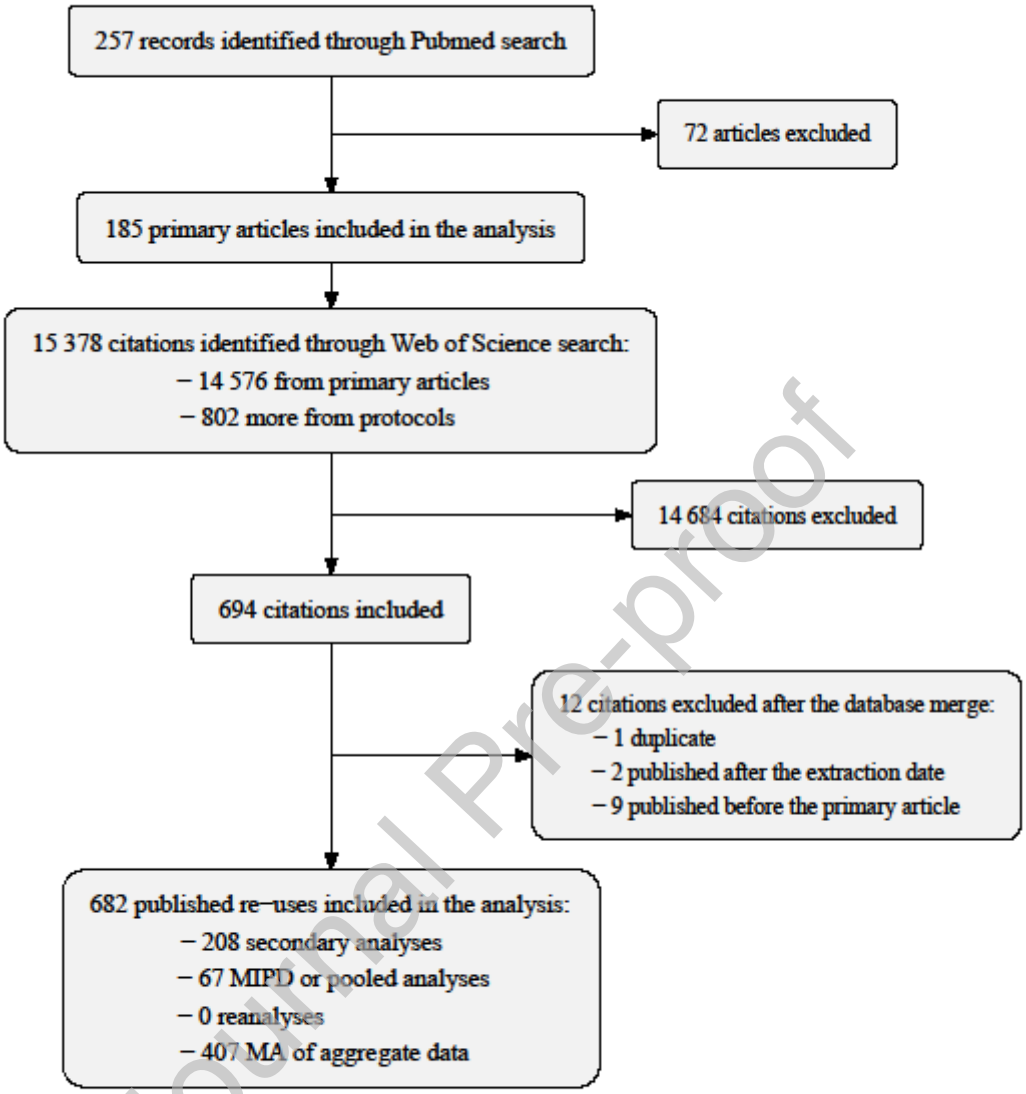

Figure 1. Study flow diagram

Figure 2

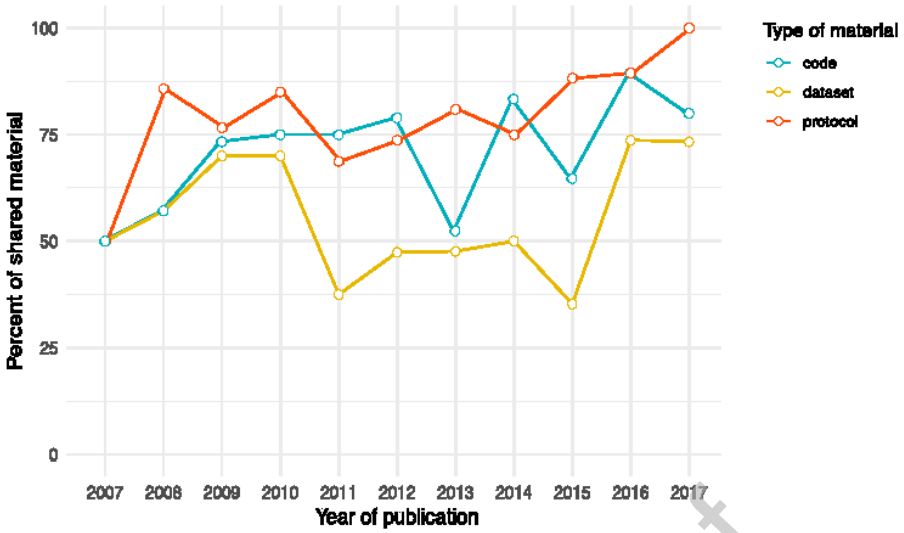

Figure 2. Data-sharing rates for protocol, statistical code and dataset of RCTs published in the Annals of Internal Medicine over time

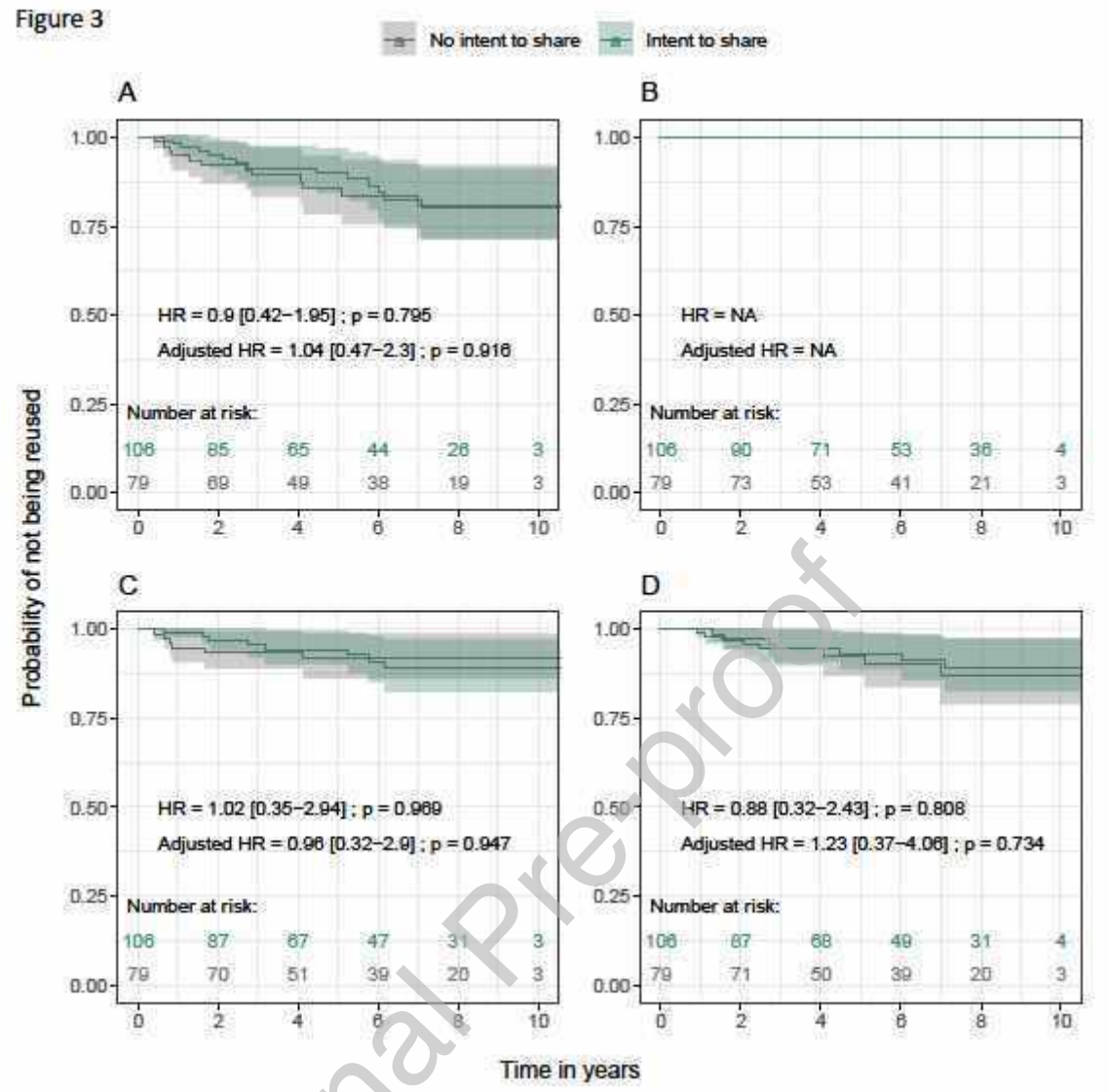

Figure 3. Kaplan-Meier curves and hazard ratios (HR) of published re-uses where the first, last and corresponding authors are not among the authors of the primary article

A: any type of published re-uses. B: published re-analyses. C: published secondary analyses. D: published MIPD.

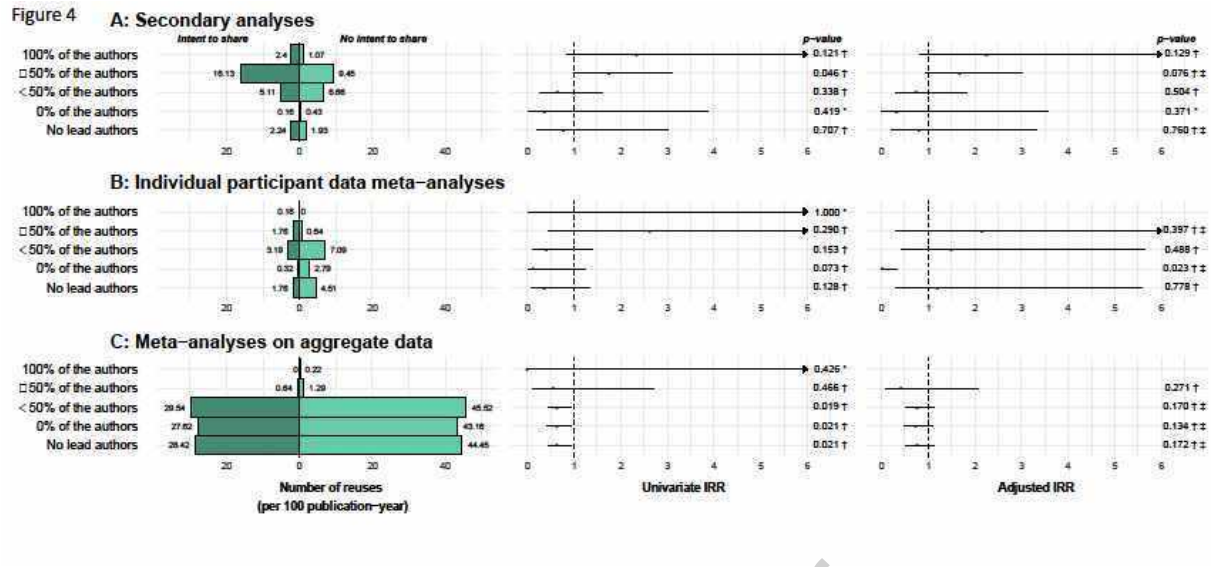

Figure 4. Number of re-uses by intent to share

**: Poisson model*
†: Binomial negative model
‡: Mixed model

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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REGISTERED REPORT

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Data-sharing and re-analysis for main studies assessed by the European Medicines Agency—a cross-sectional study on European Public Assessment Reports

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Abstract

Background: Transparency and reproducibility are expected to be normative practices in clinical trials used for decision-making on marketing authorisations for new medicines. This registered report introduces a cross-sectional study aiming to assess inferential reproducibility for main trials assessed by the European Medicines Agency.

Methods: Two researchers independently identified all studies on new medicines, biosimilars and orphan medicines given approval by the European Commission between January 2017 and December 2019, categorised as 'main studies' in the European Public Assessment Reports (EPARs). Sixty-two of these studies were randomly sampled. One researcher retrieved the individual patient data (IPD) for these studies and prepared a dossier for each study, containing the IPD, the protocol and information on the conduct of the study. A second researcher who had no access to study reports used the dossier to run an independent re-analysis of each trial. All results of these re-analyses were reported in terms of each study's conclusions, *p*-values, effect sizes and changes from the initial protocol. A team of two researchers not involved in the re-analysis compared results of the re-analyses with published results of the trial.

Results: Two hundred ninety-two main studies in 173 EPARs were identified. Among the 62 studies randomly sampled, we received IPD for 10 trials. The median number of days between data request and data receipt was 253 [interquartile range 182–469]. For these ten trials, we identified 23 distinct primary outcomes for which the conclusions were reproduced in all re-analyses. Therefore, 10/62 trials (16% [95% confidence interval 8% to 28%]) were reproduced, as the 52 studies without available data were considered non-reproducible. There was no change from the original study protocol regarding the primary outcome in any of these ten studies. Spin was observed in the report of one study.

Conclusions: Despite their results supporting decisions that affect millions of people's health across the European Union, most main studies used in EPARs lack transparency and their results are not reproducible for external researchers. Re-analyses of the few trials with available data showed very good inferential reproducibility.

Trial registration: https://osf.io/mcw3t/

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Keywords: Reproducibility of results, Clinical trial, Drug approval

Background

The influence of main studies (i.e. evidence used for drug marketing approval) as assessed by the European Medicines Agency (EMA) is paramount. These studies have a major impact on drug marketing authorisations and can change the practices of European medical practitioners and the care offered to millions of patients in the European Union. Because of the major financial conflicts of interest inherent in the evaluation of pharmaceuticals [1, 2], stakeholders are typically more confident when the results and conclusions of these studies can be verified. For a long time, however, transparency has been lacking and the individual patient data (IPD) and accompanying material (e.g. code, protocol, data analysis plan) to reproduce these analyses was unavailable. An empirical analysis suggests that only a small number of re-analyses of randomised controlled trials (RCTs) have been published to date; of these, only a minority were conducted by entirely independent authors [3]. Data-sharing enabling such re-analyses is being increasingly mandated in medicine.

And indeed, the EMA aimed to pioneer transparency in this field when, in November 2010, it decided to share all documentation received, in the wake of the first version of policy 0043 [4]. As part of its transparency policy, the EMA publishes European Public Assessment Reports (EPAR) after the European Commission's decisions on the specific medicines. These reports include, among other documents, the results of main trials [5]. In October 2014, the EMA released its policy 0070 on "publication of clinical data for medicinal products for human use" [6]. The agency describes a two-step approach. From 1st of January 2015, clinical reports on medicines submitted for marketing authorisation have been published. A second step includes the publication of IPD. A date for the implementation of this step still needs to be fixed. However, as a result of Brexit and the relocation of the EMA to the Netherlands, further developments and renovation have been stopped for the moment [7, 8]. Efforts are therefore still needed to reach full transparency in the EMA.

On the other hand, umbrella groups of biopharmaceutical companies (i.e. Pharmaceutical Research and Manufacturers of America [PhRMA] and the European Federation of Pharmaceutical Industries and Associations [EFPIA]) endorsed a commitment "to enhancing public health through responsible sharing of clinical trial data" in a manner that is consistent with 3 main principles: (i) safeguarding the privacy of patients, (ii) respecting the integrity of national regulatory systems and (iii) maintaining incentives for investment in biomedical research [9]. Despite this commitment from 2013, an audit found that data availability was reached for only 9/61 (15%) clinical trials on medicines sponsored by the pharmaceutical industry and first published between 1 July 2015 and 31 December 2015 in the top 10 journals of general and internal medicine [10]. If such low rates of data-sharing were also to be observed for main trials, it would invalidate any efforts towards reproducibility for these important studies.

However, the environment for data-sharing is changing fast. And indeed, data-sharing platforms like ViVli, YODA project, or Clinical Study Data Request are more widely used. In the fall of 2019, these platforms gathered a large number of trials sponsored by the pharmaceutical industry. These three platforms included about 8000 RCTs in November 2019 [11]. Despite this available data, re-analyses are still sparse. Among the 88 published outputs we identified resulting from data-sharing on these platforms, only 3 were re-analyses: "Restoring Study 329" by Le Noury et al. which contradicted the initial publication, a trial that was already known to be misreported [12], a re-analysis of the TORCH trial suggesting an overestimation of the treatment effect in the original study [13] and the re-analysis of the "SMART-AF" trial which came to similar conclusions to the original study [14].

As part of a global research program on reproducibility in therapeutic research (ReiTheR, funded by the French National Research Agency), we designed the present cross-sectional study to assess inferential reproducibility (i.e. when IPD is available, whether qualitatively similar conclusions can be drawn from a re-analysis of the original trials) for main studies assessed by the EMA.

Our hypothesis is that for most trials (> 95%) for which we obtain the data, the results observed on the primary outcome would be fully reproducible. However, although we planned 1 year for data collection, we are aware that after this time some data would still not be available and thus not be re-analysable. Nevertheless, the worst-case scenario for precision estimates is that 50% of the studies would be analysable and reproduced.

Methods

This is a registered report: the research protocol was peer-reviewed by the journal before the actual research took place, and it received in-principle acceptance on December 20, 2019, and was registered on January 14, 2020, on the Open Science Framework [15].

Once accepted, the editors undertake to publish the completed study if the protocol is validated even if there are statistically negative findings (i.e. study hypothesis not verified). This approach is expected to reduce issues such as publication bias [16].

Eligibility criteria

EPARs

We collected all EPARs on new authorised human medications, biosimilars and orphan medicines given a positive opinion by the Committee for Medicinal Products for Human Use (CHMP) between 1 January 2017 and 31 December 2019 and approved by the European Commission. EPARs concerning generics and hybrid medicine were excluded. Definitions concerning the different types of drugs can be found in the web appendix (Additional file 1: Table S1) [15]. The distinction between new biosimilars, new generics, new hybrid medicine, orphan medicines, or new medicines followed the CHMP Meeting Highlights [17].

Main studies

Pivotal trials are referred to as "main studies" in the different EPARs. Any main study was included, with no distinction in terms of study phase, study type, study design, or intervention.

If an indication for a drug had been refused and another indication authorised, the main study for the non-authorised indication was not considered.

Furthermore, studies with no primary outcome identified were not included and were listed as non-evaluable studies.

Search strategy

Eligible main trials

Two reviewers (MS, JG) independently extracted all names of the new medicines, biosimilars and orphan medicines approved by the CHMP and entered the information on a standard data extraction form. Afterwards, a check was performed to verify that the CHMP opinion was adopted by the European Commission [18]. Next, the reviewers identified the corresponding eligible EPARs on the EMA website [19] and independently extracted all main studies reported in these EPARs. Disagreements were resolved by discussion between the two reviewers or after referral to a third reviewer (CL or FN) until a consensus was reached.

Sample size calculation

A random sample of 62 of these main studies was selected using R (rnorm function) [20]. This sample size ensured a precision of ± 12% to estimate our primary outcome (i.e. percentage of reproducible studies, see below for a definition) in the worst-case scenario for precision estimations (i.e. if the percentage of reproducible studies is 50%).

Main study document accessibility

For all randomly sampled studies, one reviewer (JG) searched for the EudraCT number and/or the Sponsor Protocol Number, and/or any other identification information in each EPAR and identified the official sponsor of the study. If this information was lacking, the same reviewer started a wildcard search using keywords (disease, drug) from the study in the European Union Clinical Trial Register [21]. If this was not successful, the reviewer went on the websites ClinicalTrials.gov [22], International Clinical Trials Registry Portal (ICTRP), World Health Organization [23] and the International Standard Randomised Controlled Trial Number (ISRCTN) allocated by BioMedCentral [24]. If information on sponsor and study number was still lacking, the reviewer contacted the EMA.

Once the sponsor and the study number were identified, the reviewer contacted the sponsor to collect all of the following *main study documents*: (i) IPD; (ii) data analysis plan; (iii) unpublished and/or published study protocols with any date-stamped amendments; (iv) all the following dates: date of the last visit of the last patient, date of database lock (if available) and date of study unblinding; and (v) unpublished and/or published (scientific article) study reports.

To this end, the reviewer sent a standardised email (Additional file 2: Letter 1), presenting the research project with a link to the registered protocol on the Open Science Framework [15]. In order to improve the return rate, up to 4 emails were sent, the original and 3 reminder emails (with a two-week interval between them).

When asked, we indicated that the data-sharing of raw data was welcome in the form of Study Data Tabulation Model (SDTM) which was created by the Clinical Data International Standard Consortium (CDISC) [25].

In some cases, it was sufficient to contact the sponsor by e-mail; in other cases, the sponsor asked us to retrieve the data on a data-sharing platform.

In parallel the same reviewer searched for these documents on the EMA portal [26] and by inspecting the published reports (if available) identified using *open trial* [27, 28]. This process is summarised in the web appendix (Additional file 3: Figure S1).

Data extraction

The identification of main studies and the following trial characteristics were extracted from the EPARs on a standard data extraction form by two independent researchers (JG and FN). For each study, the following

information was collected: patient characteristics (e.g. percentage of women, mean age of participants, paediatric indication), study methods (e.g. type of endpoint, description for each primary endpoint) and intervention characteristics (e.g. drug). An exhaustive list of the trial characteristics extracted can be found in the web appendix (Additional file 4: Table S2).

Concerning the re-analysis, a first reviewer (JG) collected the information and collated data for the re-analysis. More specifically, the reviewer prepared a dossier with the following information for each study: (i) the protocol; (ii) all amendments to the protocol (with their dates); (iii) all the following dates: date of the last visit of the last patient, date of database lock (if available) and date of study unblinding; and (iv) the IPD. If information was still lacking, the study authors were contacted.

Strategy for re-analyses

If the IPD was not available 1 year after our initial request, we initially planned to consider the study as non-reproducible (primary outcome of our study). However, we allowed some flexibility deviations to this rule (in terms of delay) during the conduct of the study, since delays were in general longer than initially planned, including from the legal review on our side. We only considered studies as not reproducible when data was not shared entirely to reproduce the primary endpoint.

Based on the dossier prepared by the first reviewer, re-analyses of the primary outcome(s) of each study were performed by a second reviewer (MS) who had no access to study reports, journal publications, statistical analysis plan, or analytical code, in order to ensure that the analysis was as blind as possible to the primary analysis. In addition, this reviewer was instructed not to try to find these documents or the published report.

For single-blind studies or open-label studies, analyses were performed according to the first version of the protocol, because outcome switching has been documented. For double-blind studies, all re-analyses were based on the latest version of the protocol issued before database lock and unblinding. If this information was not available, the date of the last visit of the last patient was used as a proxy.

Although in therapeutic research, statistical analysis can be "routine", in some cases the re-analyses involve difficult methodological choices. An independent senior statistician (AR) was available to discuss any difficult aspect or choice in the analysis plan before the re-analysis, so as to choose the most consensual analyses (e.g. intention-to-treat population for a superiority trial).

If insufficient information concerning the main analysis was provided in the protocol, the best practices for clinical research were used, following the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH Guidelines) [29].

An analysis plan was developed for each study included and was recorded on the Open Science Framework. In the supplementary material, a table is provided with details of what was taken from the ICH guidelines in case of missing information (Additional file 5: Table S3).

Re-analyses entailed the following different steps: (i) identification of the primary outcome (and detection of outcome switching), (ii) definition of the study population, (iii) re-analysis of the primary outcome. Any change identified between the first version of the protocol and the version used for the re-analysis of the primary outcome was tracked and described.

Procedure to assess reproducibility

All results of these analyses were reported in terms of each study's (i) conclusion (positive or negative), (ii) *p*-value, (iii) effect size (and details about the outcome) and (iv) changes from the initial protocol regarding the primary outcome. Regarding point (i), a non-inferiority trial was considered positive when it showed non-inferiority.

These results were first compared with the results of the analyses reported in the EPARs and, if these were not available, with the study reports, and again if not available, with the publications. All results from all available documents were gathered (EPARs, study reports and publications) and were presented in the results section.

Because interpreting an RCT involves clinical expertise, and cannot be reduced to solely quantitative factors, an in-depth discussion between two researchers not involved in the re-analysis (JG and FN), based on both quantitative and qualitative (clinical judgement) factors, enabled a decision on whether the changes in results described quantitatively could materialise into a change in conclusions.

If these two reviewers judged that the conclusions were the same, the study results were considered as *reproduced*. If these two researchers judged that the conclusions were not the same, then the researcher in charge of the analysis (MS) was given the statistical analysis plan of the study and was asked to list the differences in terms of analysis. If he found a discrepancy between the study data analysis plan and his own analysis plan, then he corrected this discrepancy in his analysis (e.g. analysis population, use of covariates). Again, an in-depth discussion between two researchers not involved in the re-analysis (JG and FN) enabled a decision on whether the changes in results described quantitatively could materialise into a change in conclusions, and whether the differences in terms of analytical plan were understandable and acceptable. If

these two researchers judged that the conclusions were the same, the study was considered as *reproduced with verification*.

If these two researchers judged that the conclusions were not the same or that the change in the analytical plan was neither justified nor desirable, a senior statistician performed his own re-analysis. Details on this step can be found in the protocol of the registered report [15]. This process is described in the web appendix (Additional file 6: Figure S2).

Outcomes

The primary outcome is the proportion of studies where the conclusions were reproduced (yes/no; i.e. reproduced or reproduced with verification, as defined above). In case of a divergence for two or more co-primary outcomes in the same study (i.e. one analysis is reproduced and not the other(s)), the different co-primary outcomes were described independently but the whole study was considered as not reproduced. All reasons for classifying studies as non-reproducible or not reproduced were described qualitatively using a taxonomy we developed during the research process.

In addition, we described in what way the data-sharing required clarifications for which additional queries had to be presented to the authors to obtain the relevant information, to clarify labels or use, or both, and to reproduce the original analysis of the primary outcomes.

A catalogue of these queries was created, and we grouped similar clarifications for descriptive purposes to generate a list of some common challenges, and to help tackle these challenges pre-emptively in future published trials.

Concerning secondary outcomes, we described and compared the main outcomes, *p*-values and effect sizes in the re-analyses, and the analyses reported in the EPARs, the study reports and the publications, and we described discrepancies. In addition, for each paper, we assessed the presence of the following key reporting biases: selective reporting of the primary outcome and "spin" [30].

In case of outcome switching, meaning that a secondary outcome was considered as a primary outcome in the final analysis, both endpoints were to be re-analysed.

To analyse "spin" in the results observed for the primary outcome, we took the definition provided by Yavchitz et al. who described it as being "a specific way of reporting, intentional or not, to highlight that the beneficial effect of the experimental treatment in terms of efficacy or safety is greater than that shown by the results" [31].

The modalities of data-sharing were described by the following categories: the type of data-sharing, the time lapse for collecting the data, the reason for non-availability of data, the deidentification of data (i.e. 18 identifiers, as required by the Health Insurance Portability and Accountability Act) [32] and the type of the shared data (here we distinguish "computerized data" which is not formal or ordered, "cleaned data, categorized and ordered" and "analyzable data" meaning ready for analysis) [33].

Data analysis

We performed a descriptive analysis of the characteristics of the main studies extracted included in the EPARs selected. This included counts, percentages and their associated 95% confidence intervals (CIs).

Effect estimates in the different studies were expressed as standardised mean differences (SMDs) and their associated 95% CIs. For binary outcomes, odds ratios and their 95% CIs were calculated and converted into the standardised mean difference [34].

To compare the results of our re-analyses with the original results, the following steps were implemented: (i) we compared the statistical significance in the form of the *p*-value. If different, the results were considered as not reproducible. If not different, (ii) we qualitatively compared effect sizes and their respective 95% CIs. In case of $\pm$ 0.10 points difference in point estimates (expressed as standardised mean differences), the difference was discussed with a clinician in order to assess its clinical significance.

All analyses were performed using the open source statistical software R (R Development Core Team) [20] and SAS software™ .

Changes to the registered protocol

We set a 1-year deadline to obtain data. However, data demands were lengthy, and delays were in some cases produced from our side. Hence, study data that was sent after this date was included in the re-analysis process.

Furthermore, although we said we would only use R software for data analysis, SAS software was used for two studies because of its more potent approach in mixed model analyses.

For one study we were unable to calculate the odds ratio. Starting with the incidence rate ratio, we used Chinn conversion to receive obtain the SMD [35]. This approach is justified in cases where events are rare and the incidence rate ratio can be treated as an odds ratio.

Because of low data-sharing rates, one researcher checked (JG) whether data-sharing policies were posted on the companies' websites. The findings were reconfirmed by a second researcher.

Results

Study selection

The searches and consensus finished on 27 February 2020 and yielded 317 main studies identified in 173 EPARs. Of these, 25 were excluded (duplicates and studies with no primary endpoint) resulting in 292 individual studies. Of these, 62 were randomly selected (Fig. 1) and the respective data was requested from forty sponsors. All sponsors were contacted, and data was requested, either by mail or directly through a data-sharing platform. After exchanges with staff, for six datasets on Vivli, and for three on YODA, requests were issued.

Data availability

Among the 62 studies, we received IPD for 10 trials (16% [CI95 8 to 28%]) from six sponsors [36–45]. For these studies, the median number of days before data became available was 253 [interquartile range (IQR) 182–469]. For these studies, all but one of the sponsors were big pharmaceutical companies and all but one of these companies had a data-sharing policy on their website. IPD for four studies was provided via data-sharing platforms (one was provided by one sponsor on Vivli and three by a single sponsor on YODA). Three studies were shared via a remote desktop monitored by the company in possession of the data. Another three data sets from three different sponsors were sent directly to us. All IPD received was analysable and deidentified.

For the remaining 52 studies, reasons for unavailability were heterogeneous (Fig. 1). The most common reason was restriction due to the study status, i.e. extension studies were ongoing (13/52; 25%). Other reasons included confidentiality (9/52;17.3%) or lack of scientific merit as assessed by the companies' procedures. The existence of possible privacy concerns was put forward for one study as a reason for not sharing data. Of the 52 studies where IPD was not shared, 40 (77%) belonged to companies that had a data-sharing policy (Fig. 2).

Study characteristics

The characteristics of the ten studies with available IPD are presented in Table 1. The median sample size was 548 patients [IQR 278–778]. Three were single-arm studies, one was a two-arm study, four were three-arm and two were four-arm. Two involved a non-inferiority design, and for all ten studies, the primary publications, the study protocols and the study reports were retrieved.

Reproducibility

For the ten trials with available IPD, we identified 23 distinct outcomes eligible for re-analyses (relating to different comparisons and/or different primary endpoints). Detailed results of these re-analyses are presented in Fig. 3. Sixteen re-analyses (from six studies) were considered as reproduced; seven re-analyses (from five studies) were considered as reproduced with verification.

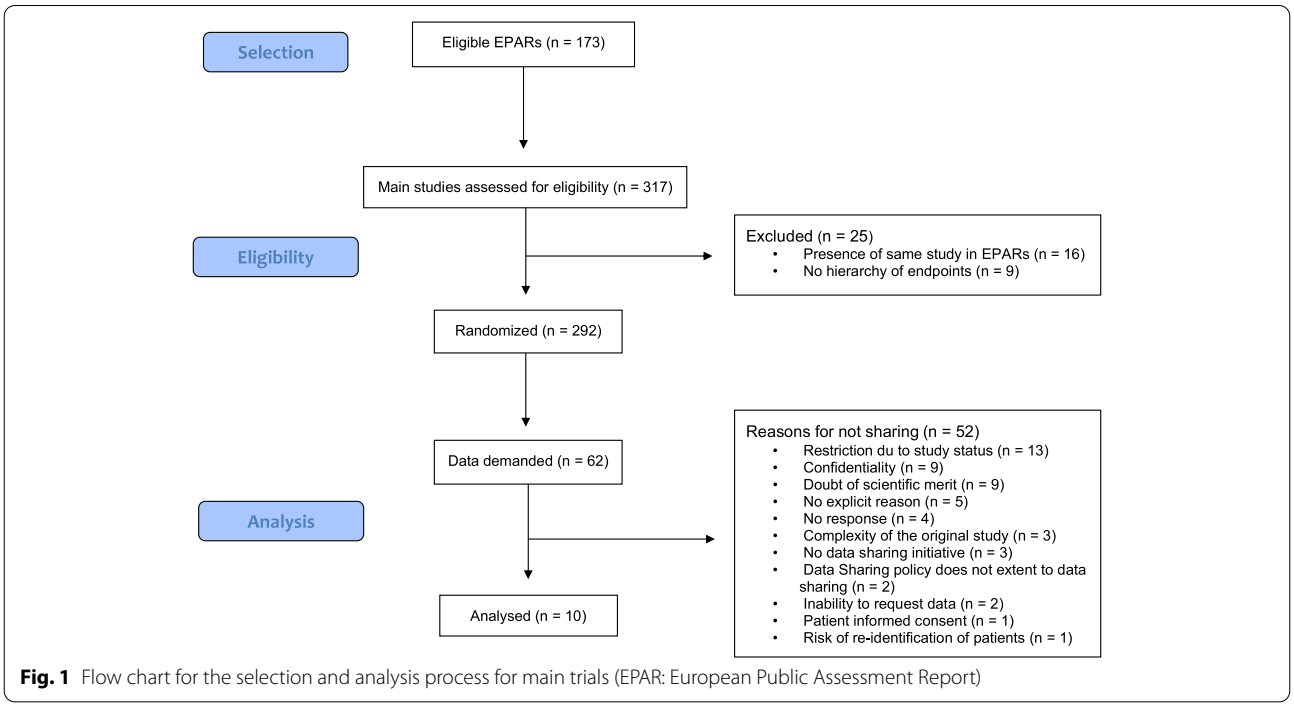

Fig. 1 Flow chart for the selection and analysis process for main trials (EPAR: European Public Assessment Report)

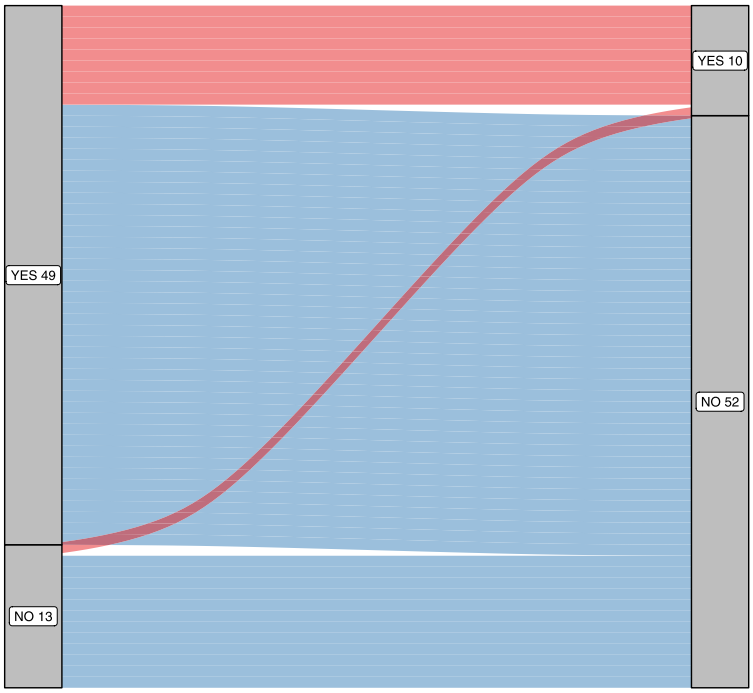

Fig. 2 Outcome of data-sharing demands in relation to data-sharing policies

The 52 studies without available data were considered as not reproducible. Therefore, for our primary outcome, the conclusions of 10/62 trials (16% [CI95 8 to 28%]) were reproduced (i.e. reproduced (n= 5) or reproduced with verification (n= 5)).

We found no selective reporting of the studies' primary outcomes and no change from the original study protocol for the primary outcome in any of these ten studies. Spin was observed in one study (see Table 2) [43].

For 9/10 studies, the results reported in the EPAR, the study report, and the publication were identical (Fig. 4). In one study [43], small numerical differences were observed, since the statistical approach required by the EMA for the EPAR (ANCOVA) was different from the approach required by the FDA (mixed model with repeated measures) and reported in the study report and the paper. In some cases, comparisons were not indicated in the paper nor in the study report (as detailed on Fig. 4).

List of challenges

Time required for data retrieval

Requesting and receiving the data was time-consuming. Interactions with sponsors were, on some occasions, lengthy, especially if several were involved on the same data-sharing platform. For example, on Vivli, we submitted a data request concerning six studies from three sponsors. The sponsors raised various questions. In one study (NCT00927498), the ownership of the data created confusion. The trial data was purchased by Pfizer. However, Vivli informed us that Pfizer was not in possession of the data and referred us back to the original Principal Investigator of the study who no longer had any rights over the data. After clarification via the platform, access was denied by Pfizer for reasons of insufficient scientific merit of our approach.

As part of the data acquisition process, the legal department of our unit had to confirm the data agreement and this step on our side was also lengthy. For two datasets, we exceeded our 1-year limit for data retrieval by 2 weeks. For three additional studies that were requested on YODA, 134 additional days were calculated. In this case, the data was not available at the time of our initial request (18/05/2020) but YODA contacted us on (04/03/2021) to indicate that the data was now on the platform and could be requested. After a request, we received this data on (14/10/2021). These studies were included in our analysis since these long time-lapses were considered as minor deviations from our initial protocol.

Incomplete datasets, metadata and further clarifications

Data dictionaries were available for 7/10 studies. In five studies, we had to contact the sponsor/platform

Table 1 Summary of studies included for which data was received

Study acronym	Study	Study drug	Comparator drug	Sponsor	Design	Study duration (weeks)	Number of arms	Participants	Percentage of women	Mean age of participants (SD)
ENDURANCE-4	Asselah, 2018 [36]	Glecaprevir/pibrentasvir	NA	AbbVie Deutschland GmbH & Co. KG	Non-controlled cohort study	24	1	121	36.4	52.66 (11)
M41008—1002,	Mrowietz, 2017 [37]	Dimethyl fumarate	Placebo/dimethyl fumarate + ethyl hydrogen fumarate	Almirall, S.A.	Superiority and non-inferiority (head to head)	16	3	699	35.3	44.2 (14.5)
ERC 231	Archer, 2015 [38]	Dehydroepiandrosterone (DHEA)	Placebo	Endoceutics	Superiority (head to head)	12	3	255	100	58.5 (6)
Clarity	Giovannoni, 2010 [39]	Cladribine	Placebo	Merck Serono International S.A.	Superiority (head to head)	96	3	1326	67.6	38.6 (10)
NN7088-3885	Trakymiene, 2020 [40]	Turoctocog Alfa pegol	NA	Novo Nordisk A/S	Non-controlled cohort study	26	1	68	0	6 (3.3)
SUSTAIN 2	Ahren, 2017 [41]	Semaglutide	Sitagliptine	Novo Nordisk A/S	Superiority and non-inferiority (head to head)	56	4	1231	49.4	55.1 (10)
SUSTAIN 5	Rodbard, 2018 [42]	Semaglutide	Placebo	Novo Nordisk A/S	Superiority (head to head)	30	4	397	43.9	58.8 (10.1)
TRANSFORM-1	Fedgchin, 2019 [43]	Esketamine	Placebo	Janssen-Cilag International NV	Superiority (head to head)	4	3	346	70.3	46.3 (11.6)
SUSTAIN-1	Daly, 2019 [45]	Esketamine	Placebo	Janssen-Cilag International NV	Superiority (head to head)	16	2	705	64.8	46.1 (11.1)
SUSTAIN-2	Wajs, 2020 [44]	Esketamine	NA	Janssen-Cilag International NV	Non-controlled cohort study	52	1	802	62.6	52.2 (13.7)

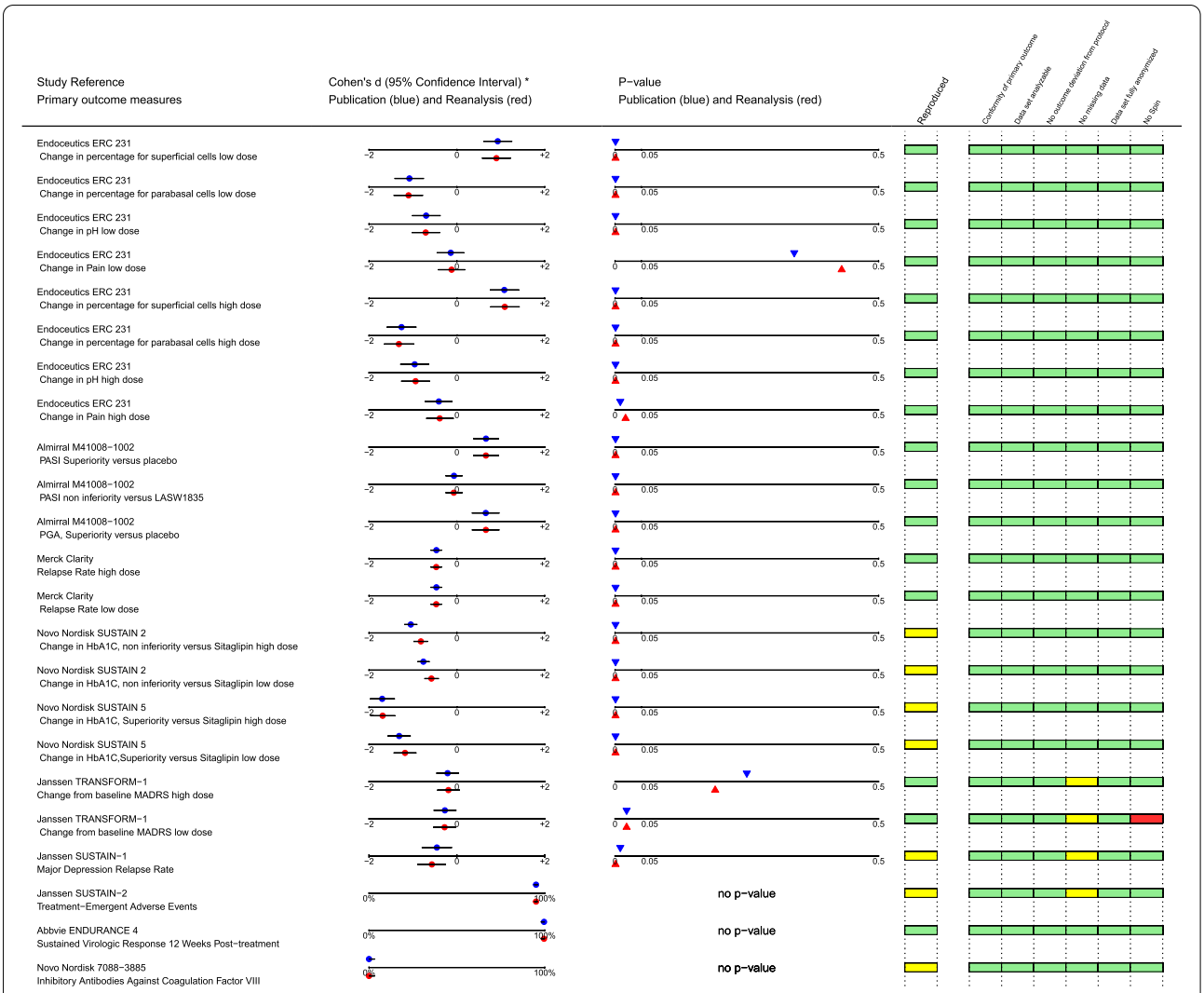

Fig. 3 Outcome of study re-analyses in terms of effect size and *p*-values, including study details (* outcomes of three studies were expressed in percentages)

Table 2 Identification of spin one of the selected studies

One study that examined the use of esketamine in treatment-resistant depression used a hierarchical testing approach: if the higher of two doses was not positive, according to the protocol the lower dose should not have been tested and reported. It was nevertheless tested and presented in the paper despite a negative result on the 84 mg dose: "*… Although esketamine 56 mg/ antidepressant could not be formally tested, the LS means difference was –4.1 [–7.67, –0.49] (nominal 2-sided P value=.027)*" and "*… Statistical significance was not achieved for the primary endpoint; nevertheless, the treatment effect (Montgomery-Asberg Depression Rating Scale) for both esketamine/antidepressant groups exceeded what has been considered clinically meaningful for approved antidepressants vs placebo [...] This study provides supportive evidence for the safety and efficacy of esketamine nasal spray as a new, rapid-acting antidepressant for patients with treatment- resistant depression.*"

to request additional data, as the data necessary to re-analyse the outcomes was missing (in three esketamine trials and in two semaglutide trials). We received additional data after 28 days in the case of the esketamine trials and were able to re-analyse the primary outcome. In the two three-arm studies from the same sponsor, comparing semaglutide with sitagliptin and placebo—non-inferiority on a primary outcome (change in HbA1c) and superiority on a "key secondary outcome" (bodyweight)—data concerning bodyweight was not available and was deleted as part of the anonymisation process. This study used a hierarchical testing

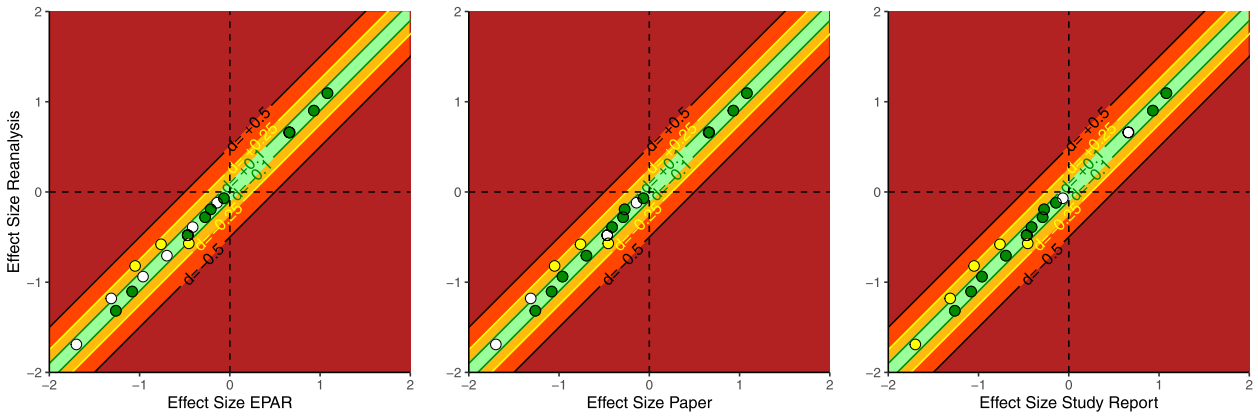

Fig. 4 Original study effect size versus replication effect size in different types of reports (d: Cohen's *d*; colour of the dots: green = outcome reproduced, yellow = outcome reproduced with verification, white = outcome not reported in this publication type; colour of the bars represent the range of differences in point estimates between re-analysis and result in publication type: light green = ± 0.10, orange = ± 0.25, light red = ± 0.50, dark red ≥ 0.50; *not including three outcomes that were expressed in percentages)

approach and we initially planned to re-analyse the outcome relating to bodyweight which was distinct from the other secondary outcomes by being included in the hierarchical approach. Still, after contacting the sponsor who pointed out that it was not strictly speaking a primary outcome, we did not consider the analysis of bodyweight any further.

Data analysis

In 2/10 cases, while we reproduced the conclusions of the studies, we did not define the same analysis population with respectively 303 and 434 vs 297 and 433 patients analysed in the studies by Janssen SUSTAIN-1 and Merck Clarity. For the latter study, discrepancy for one patient was clarified with the sponsor. In this study, one patient was counted twice due to re-screening, and to the de-anonymisation of the data which made identification impossible. This information was included in the analysis data reviewer's guide to which the authors had no access.

Among those two studies, the esketamine study published by Janssen had a very complex design involving randomised and non-randomised patients. The absence of a clear randomisation list and of a data dictionary made the re-analysis very challenging.

Two months after a request for clarification, we received the randomisation list. A close inspection of this list confirmed that we were able to correctly identify the 297 randomised patients and that we included by mistake in our analysis population six out of 600 non-randomised patients. Such discrepancy had no consequences on the conclusion of the re-analysis.

The results of the re-analysis exceeded the fixed threshold for the effect size of the primary endpoint of relapse of depressive symptoms (originally −0.45 vs −0.57 in the re-analysis) but this was considered a minor clinical difference and the study was considered as reproduced.

In studies using mixed models with repeated measures, we used SAS instead of R, reaching similar conclusions (suggested by the sponsor). However, small numerical inconsistencies were present. Again, for three outcomes in these two studies, the re-analysed effect size exceeded the prefixed threshold of 0.10 points in the effect size. However, the referees in charge (FN and JG) concluded that the differences of −1.05 vs −0.82, −0.76 vs −0.58 and −1.31 vs −1.18 for the change in HbA1c did not affect the conclusions of the study demonstrating large effect sizes in reducing HbA1c. The company in charge confirmed that due to anonymisation reproducing the exact same results would not be possible, even when providing the statistical code.

One study did not specify primary endpoints in its protocol but only objectives [44]. We double-checked the reasons for inclusion. Despite being a single-arm safety study, the trial was eligible since it was labelled as a main study in the EPAR and had primary endpoints described on ClinicalTrials.gov. The two researchers that were not involved in the study analysis decided to retain the first endpoint (treatment-emergent adverse events) over eleven primary outcomes listed on ClinicalTrials.gov for the analysis, as it was in line with the study objectives.

Discussion

Main results

Ten out of 62 main trials (16%) used by the EMA in its approval processes were reproduced. When IPD was available, all re-analyses largely reproduced the original results. These results are in line with an earlier survey of RCTs published by *PLOS Medicine* and *The BMJ*

[46]. However, lack of IPD availability hampered our reproducibility effort for most of the trials, despite the fact that a large majority of sponsors had a data-sharing policy. It is clear that while pharmaceutical companies have signed on to the principles of data-sharing, they have not implemented this practice. Certain trials had extension phases, which, in the sponsors' view, justified the non-data-sharing before study completion. Similar issues regarding the timing of the release of IPD have recently been described for COVID-19 vaccine trials [47].

These delays, rather like an embargo, could impact the possibility for independent researchers to perform timely re-analyses. Even for trials sharing IPD, times for requests and receipt of data were quite long. Another reason for non-availability of sharing was "lack of scientific merit" as assessed by the companies' procedures. Interestingly, we intentionally adopted the registered report format for this paper, in order to pre-emptively address this potential concern: this publication process enabled a thorough and independent peer review of its "scientific merit" prior to data collection and analysis.

If the scientific merit of any data re-use is surely important when it comes to responsible sharing of IPD, it is however a subjective and arbitrary notion. Furthermore, there was no agreement on this point for our request, as some sponsors, including those with independent procedures (e.g. those sharing on YODA), agreed to share their data. It is likely that sponsors are less inclined to share their data for the purpose of a re-analysis. A survey of trialists suggested that willingness to share data could depend on the intended reuse of the data, with 97% of respondents willing to share data for a meta-analysis vs 73% for a re-analysis [48]. One additional explanation could be the fear of data misuse [49]. In addition, in the field of clinical trials, there is currently no systematic culture of reproducibility and independent re-analyses of clinical trials remain sparse in the published literature [3].

Limitations

Caution is needed before generalising these results to other trials. Our results are focused on a very selective sample of trials, i.e. main studies submitted to the EMA. These studies (mostly from Europe) are larger than the average published RCT in the medical literature [50] and all were sponsored by the pharmaceutical industry. Implementation of data-sharing policies, although not optimal, is likely better than implementation by public funders [51]. In addition, we selected trials labelled as main studies (pivotal trials) in the EMA dossier and other studies could have been selected from the EPAR, i.e. the so-called supportive trials. Although less important, those supportive trials could have different characteristics from the main studies we included.

Low rates of data-sharing limited our ability to explore other inferential reproducibility issues in detail. In line with our registered protocol, 52 trials were categorised as non-reproducible because data-sharing was denied. In our definition, we considered that without the data, the results cannot be reproduced. However, the results of these missing studies could be reproducible if their individual patient data was available. The main result of our study is therefore that data-sharing is not implemented. In an ongoing complementary registered report that received in-principle acceptance in Royal Society Open Science [52], we have already received an agreement for 90% of 62 studies randomly selected on the main data-sharing platforms (Vivli, YODA and CSDR). These results will enable a triangulation of evidence on the reproducibility of therapeutic research.

Another limitation of our study is that it was restricted to primary endpoints. While primary endpoints are paramount in main trials, other endpoints (e.g. secondary endpoints and/or safety endpoints) could also be of interest to regulators. Furthermore, numerical differences, observed in some re-analyses, could be caused by the choices of the researcher in charge, and do not necessarily mean that the original estimates were wrong.

Finally, while we tried to ensure as far as possible that the re-analyst was blind to study results, some bias could have applied to the researcher in charge of re-analysing the data, as he was aware that the studies were part of authorised MAAs, which tend to be significantly "positive", and indeed, all but one of the trials included were "positive".

Perspectives

Unlike the FDA, the EMA does not conduct independent re-analyses, making re-analyses by independent researchers even more important. Possibly, for these trials, the application of data-sharing policies should not rely only on the sponsor, and appropriate policies should be adopted by the regulatory authorities. While the EMA has demonstrated openness towards the idea of transparency with its implementation of 0043 policies and the first step in the even more progressive 0070 policy [53], more action is needed to ensure that data is effectively shared. Phase 2 of the EMA 0070 policy foresees the sharing of IPD, but there is no clear timeline yet. Our results support the urgent need to adopt, implement and monitor this policy.

In addition, efforts towards transparency and data-sharing could be incentivised. Success stories like the Good Pharma Score Card show that data-sharing rates rise when sponsors are made aware of its inaccessibility

[54]. We have recently proposed the concept of registered drug approvals, an open science pathway for drug marketing authorisation which could incentivise data-sharing, among other open sciences practices [55].

Conclusions

Data-sharing practices are rare for re-analyses of clinical trials for the authorisation of medication in Europe, even for sponsors with data-sharing policies. As a consequence, most main studies used in EPARs lack transparency and their results are not reproducible for external researchers, although their results support decisions that affect millions of people's health across the European Union. Nonetheless, here re-analyses of the few trials with available data showed good inferential reproducibility. Our data provides a baseline for data-sharing implementation in these main studies. Europe strongly supports Open Science and transparency [56], it is therefore critical to develop interventions that increase data-sharing for these main studies, and to monitor improvements in the EMA data in the next few years.

Abbreviations

AdAM: Analysis data model; BMJ: The British Medical Journal; CDAS: Clinical Data Acquisition Standards Harmonisation; CDISC: Clinical Data International Standard Consortium; CHMP: Committee for Medicinal Products for Human Use; CI: Confidence interval; EFPIA: European Federation of Pharmaceutical Industries and Associations; EMA: European Medicines Agency; EPAR: European Public Assessment Report; EudraCT: European Union Drug Regulation Authorities Clinical Trials; ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; ICTRP: International Clinical Trials Registry Portal; IPD: Individual patient data; ISRCTN: International Standard Randomised Controlled Trial Number; MAA: Marketing authorisation application; PhRMA: Pharmaceutical Research and Manufacturers of America; PLOS: Public Library of Science; RCT: Randomised controlled trial; ReiTheR: Reproducibility in therapeutic research; SDTM: Study Data Tabulation Model; SMD: Standardised mean difference.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-022-02377-2.

Additional file 1: Table S1 Definitions of different types of medication on the EMA website.

Additional file 2: Letter S1 Letter to the Sponsor.

Additional file 3: Figure S1 Process of accessing main study documents.

Additional file 4: Table S2 Study Characteristics extracted.

Additional file 5: Table S3 Details of information extracted from the ICH guidelines in case of missing information.

Additional file 6: Figure S2 Procedure for assessing reproducibility.

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Authors' contributions

MS, JG and FN designed the work. MS and JG extracted the data. MS performed the experiments and analysed the data. MS and FN wrote the first draft of the manuscript. AR, BL, CL and DM read the article and substantively revised it. All authors read and approved the final manuscript.

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Availability of data and materials

Data and code that supports the findings of this study is made available on our link to the Open Science Framework (https://osf.io/mcw3t/). Furthermore, the pre-registered SAPs for the data analyses and a guide on how to demand IPD from the studies can be found under the link indicated above. Furthermore, interested researchers can contact the corresponding author via mail. IPD of the respective re-analysed studies cannot be shared directly but should be requested to the corresponding sponsor.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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References

1. Als-Nielsen B, Chen W, Gluud C, Kjaergard LL. Association of funding and conclusions in randomized drug trials: a reflection of treatment effect or adverse events? JAMA. 2003;290(7):921–8.
2. Djulbegovic B, Lacevic M, Cantor A, Fields KK, Bennett CL, Adams JR, et al. The uncertainty principle and industry-sponsored research. Lancet. 2000;356(9230):635–8.
3. Ebrahim S, Sohani ZN, Montoya L, Agarwal A, Thorlund K, Mills EJ, et al. Reanalyses of randomized clinical trial data. JAMA. 2014;312(10):1024–32.
4. European Medicines Agency. European Medicines Agency policy on access to documents. 2018. [cited 2019 July 05]. Available from: https://www.ema.europa.eu/en/documents/other/policy/0043-european-medicines-agency-policy-access-documents_en.pdf.
5. European Medicines Agency. Guide to information on human medicines evaluated by EMA. 2017. Available from: https://www.ema.europa.eu/en/documents/other/guide-information-human-medicines-evaluated-european-medicines-agency-what-agency-publishes-when_en.pdf.

6. European Medicines Agency. European Medicines Agency policy on publication of clinical data for medicinal products for human use. 2019. Available from: https://www.ema.europa.eu/en/documents/other/european-medicines-agency-policy-publication-clinical-data-medicinal-products-human-use_en.pdf.
7. European Medicines Agency. Clinical data publication 2019 [cited 2019 June 24]. Available from: https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/clinical-data-publication.
8. Doshi P. EMA scales back transparency initiatives because of workload. BMJ. 2018;362:k3513.
9. Pharmaceutical Research and Manufacturers of America. PhRMA Principles ForResponsible ClinicalTrial DataSharing 2013. Available from: http://phrma-docs.phrma.org/sites/default/files/pdf/PhRMAPrinciplesForResponsibleClinicalTrialDataSharing.pdf.
10. Hopkins AM, Rowland A, Sorich MJ. Data sharing from pharmaceutical industry sponsored clinical studies: audit of data availability. BMC Med. 2018;16(1):165.
11. Ohmann C, Moher D, Siebert M, Motschall E, Naudet F. Status, use and impact of sharing Individual Participant Data from clinical trials: a scoping review; 2019.
12. Le Noury J, Nardo JM, Healy D, Jureidini J, Raven M, Tufanaru C, et al. Restoring Study 329: efficacy and harms of paroxetine and imipramine in treatment of major depression in adolescence. BMJ. 2015;351:h4320.
13. Muff S, Puhan MA, Held L. Bias away from the null due to miscounted outcomes? A case study on the TORCH trial. Stat Methods Med Res. 2018;27(10):3151–66.
14. Gay HC, Baldridge AS, Huffman MD. Feasibility, process, and outcomes of cardiovascular clinical trial data sharing: A Reproduction Analysis of the SMART-AF Trial. JAMA Cardiol. 2017;2(12):1375–9.
15. Open Science Framework. Maximilian Siebert 2019. Available from: https://osf.io/mcw3t/.
16. Hardwicke TE, Ioannidis JPA. Mapping the universe of registered reports. Nat Hum Behav. 2018;2(11):793–6.
17. European Medicines Agency. CHMP: Agendas, minutes and highlights 2019. [cited 2019 June 26]. Available from: https://www.ema.europa.eu/en/committees/chmp/chmp-agendas-minutes-highlights.
18. European Commission. Public Health - Union Register of medicinal products 2019. [cited 2019 June 26]. Available from: http://ec.europa.eu/health/documents/community-register/html/index_en.htm.
19. European Medicines Agency. Medicines 2019 [cited 2019 June 26]. Available from: https://www.ema.europa.eu/en/medicines.
20. R Core Team. R. A language and environment for statistical computing. Vienna: R Foundation for Statistical Computing; 2018.
21. European Medicines Agency. EU Clinical Trials Register 2019 June 25. [cited 2019 June 26]. Available from: https://www.clinicaltrialsregister.eu/ctr-search/search.
22. U.S. National Library of Medicine. ClinicalTrials.gov 2019 [cited 2019 June 26]. Available from: https://clinicaltrials.gov/ct2/search.
23. World Health Organization. International Clinical Trials Registry Platform Search Portal 2019 [cited 2019 June 26]. Available from: http://apps.who.int/trialsearch/.
24. BioMedCentral. ISRCTN registry 2019 [cited 2019 June 26]. Available from: http://www.isrctn.com/.
25. Hume S, Chow A, Evans J, Malfait F, Chason J, Wold JD, et al. CDISC SHARE, a global, cloud-based resource of machine-readable CDISC standards for clinical and translational research. AMIA Jt Summits Transl Sci Proc. 2018;2017:94–103.
26. European Medicines Agency. Clinical Data 2019 [cited 2019 June 26]. Available from: https://clinicaldata.ema.europa.eu/web/cdp/home.
27. Goldacre B, Gray J. OpenTrials: towards a collaborative open database of all available information on all clinical trials. Trials. 2016;17:164.
28. Open Knowledge International, Data Lab. OpenTrials 2019 [cited 2019 June 26]. Available from: https://opentrials.net/.
29. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. Welcome to the ICH official website 2019 [cited 2019 June 25]. Available from: https://www.ich.org/home.html.
30. Chiu K, Grundy Q, Bero L. 'Spin' in published biomedical literature: a methodological systematic review. PLoS Biol. 2017;15(9):e2002173.
31. Yavchitz A, Boutron I, Bafeta A, Marroun I, Charles P, Mantz J, et al. Misrepresentation of randomized controlled trials in press releases and news coverage: a cohort study. PLoS Med. 2012;9(9):e1001308.
32. U.S. Department of Health & Human Services. Guidance regarding methods for de-identification of protected health information in accordance with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule 2012 [cited 2019 November 20]. Available from: https://www.hhs.gov/hipaa/for-professionals/privacy/special-topics/de-identification/index.html.
33. Zarin DA, Tse T. Sharing individual participant data (IPD) within the context of the trial reporting system (TRS). PLoS Med. 2016;13(1):e1001946.
34. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. Introduction to meta-analysis. West Sussex: Wiley; 2009.
35. Chinn S. A simple method for converting an odds ratio to effect size for use in meta-analysis. Stat Med. 2000;19(22):3127–31.
36. Asselah T, Kowdley KV, Zadeikis N, Wang S, Hassanein T, Horsmans Y, et al. Efficacy of glecaprevir/pibrentasvir for 8 or 12 weeks in patients with hepatitis C virus genotype 2, 4, 5, or 6 infection without cirrhosis. Clin Gastroenterol Hepatol. 2018;16(3):417–26.
37. Mrowietz U, Szepietowski JC, Loewe R, van de Kerkhof P, Lamarca R, Ocker WG, et al. Efficacy and safety of LAS41008 (dimethyl fumarate) in adults with moderate-to-severe chronic plaque psoriasis: a randomized, double-blind, Fumaderm®- and placebo-controlled trial (BRIDGE). Br J Dermatol. 2017;176(3):615–23.
38. Archer DF, Labrie F, Bouchard C, Portman DJ, Koltun W, Cusan L, et al. Treatment of pain at sexual activity (dyspareunia) with intravaginal dehydroepiandrosterone (prasterone). Menopause. 2015;22(9):950–63.
39. Giovannoni G, Comi G, Cook S, Rammohan K, Rieckmann P, Sørensen PS, et al. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. N Engl J Med. 2010;362(5):416–26.
40. Šaulytė Trakymienė S, Economou M, Kenet G, Landorph A, Shen C, Kearney S. Long-term safety and efficacy of N8-GP in previously treated pediatric patients with hemophilia A: final results from pathfinder5. J Thromb Haemost. 2020;18(S1):15–25.
41. Ahrén B, Masmiquel L, Kumar H, Sargin M, Karsbøl JD, Jacobsen SH, et al. Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as an add-on to metformin, thiazolidinediones, or both, in patients with type 2 diabetes (SUSTAIN 2): a 56-week, double-blind, phase 3a, randomised trial. Lancet Diabetes Endocrinol. 2017;5(5):341–54.
42. Rodbard HW, Lingvay I, Reed J, de la Rosa R, Rose L, Sugimoto D, et al. Semaglutide added to basal insulin in type 2 diabetes (SUSTAIN 5): a randomized, controlled trial. J Clin Endocrinol Metab. 2018;103(6):2291–301.
43. Fedgchin M, Trivedi M, Daly EJ, Melkote R, Lane R, Lim P, et al. Efficacy and safety of fixed-dose esketamine nasal spray combined with a new oral antidepressant in treatment-resistant depression: results of a randomized, double-blind, active-controlled study (TRANSFORM-1). Int J Neuropsychopharmacol. 2019;22(10):616–30.
44. Wajs E, Aluisio L, Holder R, Daly EJ, Lane R, Lim P, et al. Esketamine nasal spray plus oral antidepressant in patients with treatment-resistant depression: assessment of long-term safety in a phase 3, open-label study (SUSTAIN-2). J Clin Psychiatry. 2020;81(3):19m12891. https://doi.org/10.4088/JCP.19m12891.
45. Daly EJ, Trivedi MH, Janik A, Li H, Zhang Y, Li X, et al. Efficacy of esketamine nasal spray plus oral antidepressant treatment for relapse prevention in patients with treatment-resistant depression: a randomized clinical trial. JAMA Psychiatry. 2019;76(9):893–903.
46. Naudet F, Sakarovitch C, Janiaud P, Cristea I, Fanelli D, Moher D, et al. Data sharing and reanalysis of randomized controlled trials in leading biomedical journals with a full data sharing policy: survey of studies published in The BMJ and PLOS Medicine. BMJ. 2018;360:k400.
47. Tanveer S, Rowhani-Farid A, Hong K, et al. Transparency of COVID-19 vaccine trials: decisions without data. BMJ Evid Based Med. 2021. https://doi.org/10.1136/bmjebm-2021-111735.
48. Tannenbaum S, Ross JS, Krumholz HM, Desai NR, Ritchie JD, Lehman R, et al. Early experiences with journal data sharing policies: a survey of published clinical trial investigators. Ann Intern Med. 2018;169(8):586–8.
49. Rathi V, Dzara K, Gross CP, Hrynaszkiewicz I, Joffe S, Krumholz HM, et al. Sharing of clinical trial data among trialists: a cross sectional survey. BMJ Br Med J. 2012;345:e7570.
50. Chan A-W, Altman DG. Epidemiology and reporting of randomised trials published in PubMed journals. Lancet. 2005;365(9465):1159–62.
51. Gaba JF, Siebert M, Dupuy A, Moher D, Naudet F. Funders' data-sharing policies in therapeutic research: a survey of commercial and non-commercial funders. PLoS One. 2020;15(8):e0237464.

52. Gaba J, Siebert M, Renault A, Laviolle B, Locher C, Moher D, et al. Inferential reproducibility of therapeutic research: a cross-sectional study of randomized controlled trials available on major data-sharing platforms 2020. Available from: https://osf.io/dw8et/.
53. Egilman AC, Kapczynski A, McCarthy ME, Luxkaranayagam AT, Morten CJ, Herder M, et al. Transparency of regulatory data across the European Medicines Agency, Health Canada, and US Food and Drug Administration. J Law Med Ethics. 2021;49(3):456–85.
54. Bioethics International. Good Pharma Scorecard 2021. Available from: https://bioethicsinternational.org/good-pharma-scorecard/.
55. Naudet F, Siebert M, Boussageon R, Cristea IA, Turner EH. An open science pathway for drug marketing authorization—registered drug approval. PLoS Med. 2021;18(8):e1003726.
56. https://ec.europa.eu/info/research-and-innovation/strategy/strategy-2020-2024/our-digital-future/open-science_en

Publisher's Note

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Titre : Reproductibilité de la recherche thérapeutique : le rôle des financeurs et réanalyse d'essais cliniques via des plateformes de partage

Mots clés : Transparence de la recherche, reproductibilité, partage de données, essais cliniques

Résumé : Cette thèse explore plusieurs facettes de la reproductibilité de la recherche thérapeutique, en s'intéressant aux initiatives d'ouverture et de partage de données mis en place pour endiguer la « crise de la reproductibilité » que connait la recherche en général et plus particulièrement la recherche biomédicale. Nous nous sommes intéressés aux politiques de partage de données des financeurs, et à l'impact de ces politiques sur la disponibilité, le partage et la réutilisation des données issues d'essais cliniques. Les indicateurs de disponibilité étudiés relèvent que les politiques actuelles sont inefficaces pour garantir un partage effectif des données. Les financeurs devraient adopter une politique plus forte sur le partage de données, incluant des méthodes d'évaluation, pour s'assurer que les objectifs du partage sont atteints, le tout appuyé par des actions concertées et conjointes avec les acteurs de l'écosystème scientifique tels que les chercheurs et le système éditorial scientifique.

Nous avons également exploré la reproductibilité en recherche thérapeutique. Les données d'un échantillon aléatoire de 62 essais cliniques ont été demandées via des plateformes de partage puis réanalysées. Nous présentons ici les premiers résultats. Les résultats préliminaires portent sur 21 essais cliniques randomisés, dont la reproductibilité inférentielle a été évaluée. Les critères de jugements ont été reproduit à 85.7%.

Les conclusions de cette thèse visent à informer les acteurs de la recherche et à contribuer à l'amélioration des politiques de données ainsi que des pratiques, qui cherchent à faire progresser la recherche thérapeutique vers plus de transparence et une meilleure reproductibilité.

Title: Reproducibility in therapeutic research: Funders' role and reanalysis of clinical trials available on data sharing platforms

Keywords: Research transparency, reproducibility, open science, data sharing, clinical trials

Abstract: This thesis explores several facets necessary for the reproducibility of therapeutic research, by focusing on the initiatives of openness and data sharing put in place to stem the "crisis of reproducibility" experienced by research in general and more particularly biomedical research.

We looked at the data sharing policies of funders, and the impact of these policies on the availability, sharing and reuse of data from clinical trials. The studied availability indicators show that current policies are ineffective in ensuring effective data sharing. Funders should adopt a stronger policy on data sharing, including evaluation methods, to ensure that the objectives of sharing are met, all supported by concerted and joint actions with stakeholders such as researchers and the scientific editorial system.

We also explored reproducibility in therapeutic research. Data from a random sample of 62 clinical trials were requested via data sharing platforms and then re-analysed. Here we present the first results. The preliminary results relate to 21 randomized clinical trials whose inferential reproducibility has been assessed. The primary outcomes of the reanalysed trials were reproduced at 85.7%.

The conclusions of this thesis aim to enlighten research actors and contribute to the improvement of data policies as well as practices, which seek to advance therapeutic research towards more transparency and better reproducibility.