Clinical Trial Transparency in France
Mapping unreported drug trials

Paris (France) and Bristol (UK), March 16th 2021

"We advocate full transparency of which clinical trials are ongoing and ensuring all results are disclosed in a timely manner… full transparency on results advances both scientific understanding and timelines for product development and ultimately enables access to essential medicines."

Dr Tedros Adhanom Ghebreyesus, World Health Organisation

"Lack of transparency in clinical trials harms patients. The timely posting of summary results is an ethical and scientific obligation."

Transparency International and Cochrane

"Legislation or supporting regulations [should include] sanctions if a clinical trial is not registered and/or results are not reported."

WHO Transparency and Accountability Assessment Tool

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FOREWORD

"The health crisis that is currently shaking the whole world has unfortunately contributed to fuelling citizens' mistrust of public institutions. Under the pressure of urgency, the requirement for transparency has sometimes been relegated to the background, whether in the development of public decisions or in the communication of scientific and medical findings. However, without claiming to solve everything, transparency is undoubtedly part of the solutions to the problem, especially in times of crisis, and the importance of more transparent decision-making processes must be reaffirmed, as it is the precondition for accountability.

In an area as essential as that of clinical trials, transparency is still far from being a concrete reality in France, even though it is a regulatory obligation. This is demonstrated by this report by TranspariMED, with which Transparency International France and Mélanome France have joined forces. This rigorous study reveals that the gaps in the publication of the headline results of clinical drug trials are not evenly distributed between public and private actors, that some actors are further ahead than others. This proves that there is room for improvement. The objective of this report is not to practice a sterile 'name and shame', but to raise awareness among stakeholders, clinical trial sponsors, investigators, regulatory authorities (HAS, ANSM), pharmacovigilance centres, and academic researchers. This will allow for a constructive dialogue with civil society in order to achieve more transparency.

Beyond the simple issue of compliance with applicable European and national legal frameworks, the transparency of clinical trials is an ethical and scientific requirement provides tangible benefits.

It accelerates medical research by enabling the faster pooling of results, and allows patients to benefit from the best treatment options as soon as possible. It optimizes the allocation of public funding (research tax credits, health insurance, regional intervention funds, credits from the recovery plan, public purchases, etc.) and makes it possible to verify the proper use of public funds by actors, both public and private. It prevents bad research practices by providing access to key study parameters. It allows health agencies to make informed decisions favourable to the well-being of the population.

Importantly, clinical trials are only one link in the complex chain that forms the healthcare system. The pandemic we are going through has shown both the importance of establishing cooperation between the public and private actors who form the healthcare system, and the need to be fully transparent about the interactions between them. These links can give rise to conflicts of interest which must be managed to prevent them from distorting the decision-making process. This is what we know for sure at the end of the Mediator trial before the Paris Criminal Court, which is about to deliver, on March 29, 2021, a judgment awaited by the 6,500 civil parties in particular.

Yet even when a legal framework exists, it is often implemented incompletely, as we can see in the case of clinical trials. The Mediator trial and the Dépakine (valproate) trial, and the worldwide health scandal of the 'Implant Files' (insulin pumps, breast implants, pacemakers, prostheses) revealed by the International Consortium of Investigative Journalists in November 2018, are tragic and hence unacceptable illustrations of such failures.

The coalition work initiated around the publication of this report lays the foundations for a method that we intend to pursue in the field of health. It is by bringing together civil society actors that we will finally be able to achieve significant progress on the transparency of our health system, and guarantee everyone's health, the proper use of public funds and secure access to technical progress.**"**

Patrick Lefas
President of Transparency International France

1 KEY FINDINGS AND RECOMMENDATIONS

Obligation to report the results of all trials

Failure to report clinical trial results is not a victimless crime. It has substantial negative consequences for patients and public health. European Union (EU) rules adopted in July 2014 require the sponsors (organisations that conduct a trial) of each clinical trial registered on the EU Clinical Trials Register to post those trials' summary results to the registry within 12 months of trial completion (6 months for paediatric trials). These rules also apply to trials completed before 2014 and apply irrespective of whether a trial's outcomes have been published in the academic literature. Thus, all of the clinical trials identified in this report as missing summary results are in violation of European Union transparency rules that were designed to protect the interests of patients and taxpayers.

Key findings

The data presented in this report reflect EU Trials Tracker data from 04 February 2021, covering the largest (by numbers of drug trials launched) 33 clinical trial sponsors headquartered in France. The 33 largest French sponsors have between them registered 2,420 clinical trials of investigational medicinal products on the EU Clinical Trial Register. Some of these trials are ongoing, others have been completed. Sponsors have the obligation to send a notification to the national medicines regulator when each drug trial ends and then, 12 months later, upload the results of that trial to the registry.

- **French trial sponsors have failed to make an estimated 637 trial results public** on the European register. Because many sponsors neglect to keep their data on the register up to date, only 155 of those missing trial results are clearly identifiable. On the positive side, French sponsors have uploaded results for 371 verifiably due trials onto the registry.
- **French non-commercial sponsors perform far worse than industry.**
    - The largest pharmaceutical companies in France perform strongly. ***Servier*** and ***Ipsen*** have made every single one of their due trial results public.
    - Nearly all French public and non-profit trial sponsors perform very weakly.
- **15 out of 20 French institutions running Covid drug trials**[1] **are currently in violation of transparency rules.** Only one Covid trial sponsor has a strong compliance record.

Recommendations

- **The French Ministry of Health** should review the UK's national clinical trial transparency strategy and explore the possibility of adopting a similar approach in France.
- **The Agence Nationale de Sécurité du Médicament (ANSM)** should contact trial sponsors whose results are overdue, ensure that data on the register is consistent and accurate, monitor compliance, and develop a mechanism for routinely and automatically imposing sanctions as soon as the EU Clinical Trials Regulation becomes national law in late 2021.
- **The Centre National de la Recherche Scientifique (CNRS)** should sign up to the WHO Joint Statement. **Inserm** should fully implement its existing transparency commitments.
- **French medical research institutions** should establish central oversight over their clinical trial portfolios, adopt policies that reflect WHO best practices, and upload missing clinical trial results as rapidly as possible. See here for useful tools.

[1] French sponsors are running additional Covid trials that do not fall under EU reporting rules. Those trials fall outside the scope of this report (see methodology section). A complete list of all Covid trials is available for download on the Covid-19 TrialsTracker website.

2 PHARMA INDUSTRY VERSUS NON-COMMERCIAL INSTITUTIONS

French pharmaceutical companies perform far better overall than non-commercial trial sponsors.

COMMERCIAL TRIAL SPONSORS

The list of the 33 institutions most active in clinical drug research in France includes six commercial clinical trial sponsors: five pharmaceutical companies and one joint venture. Together, these six commercial players have sponsored 1,096 clinical trials. Out of these trials, 367 were verifiably completed more than a year ago and should thus have results publicly available on the European trial registry. The companies running these trials have made 360 of those results (98%) public. Only 7 results of industry trials (less than 2%) are verifiably missing.

Servier and ***Ipsen*** have a perfect compliance record, as does the Sanofi Pasteur MSD joint venture.[2] ***AB Science*** is the only major commercial trial sponsor that disappoints. According to registry data, the company has failed to report 5 clinical trial results; the actual figure is likely to be even higher because much of AB Science's trial data is inconsistent or out of date (see AB Science's portfolio here).

Sponsor	Trials total	Results due	With results	No results
Sanofi	682	179	178	1
Servier	144	66	66	0
Pierre Fabre	118	68	67	1
Ipsen	89	39	39	0
AB Science	34	5	0	5
Sanofi Pasteur MSD	29	10	10	0
TOTAL	**1096**	**367**	**360**	**7**

NON-COMMERCIAL TRIAL SPONSORS

Non-commercial trial sponsors in France perform far worse than their industry counterparts. Out of the 27 public and non-profit sponsors assessed, none has a good transparency record.

The table below shows the registry data for ***AP-HP***, which is by far the largest non-profit trial sponsor in France, and aggregated data for the other 26 sponsors. These sponsors have collectively launched 1,324 drug trials, more than industry. Of their 159 trials that were verifiably completed more than a year ago, only 11 trials (less than 7%) have results available on the registry.

Sponsor	Trials total	Results due	With results	No results
Assistance Publique – Hôpitaux de Paris	307	28	1	27
All 26 other con-commercial sponsors	1017	131	10	121
TOTAL	**1324**	**159**	**11**	**148**

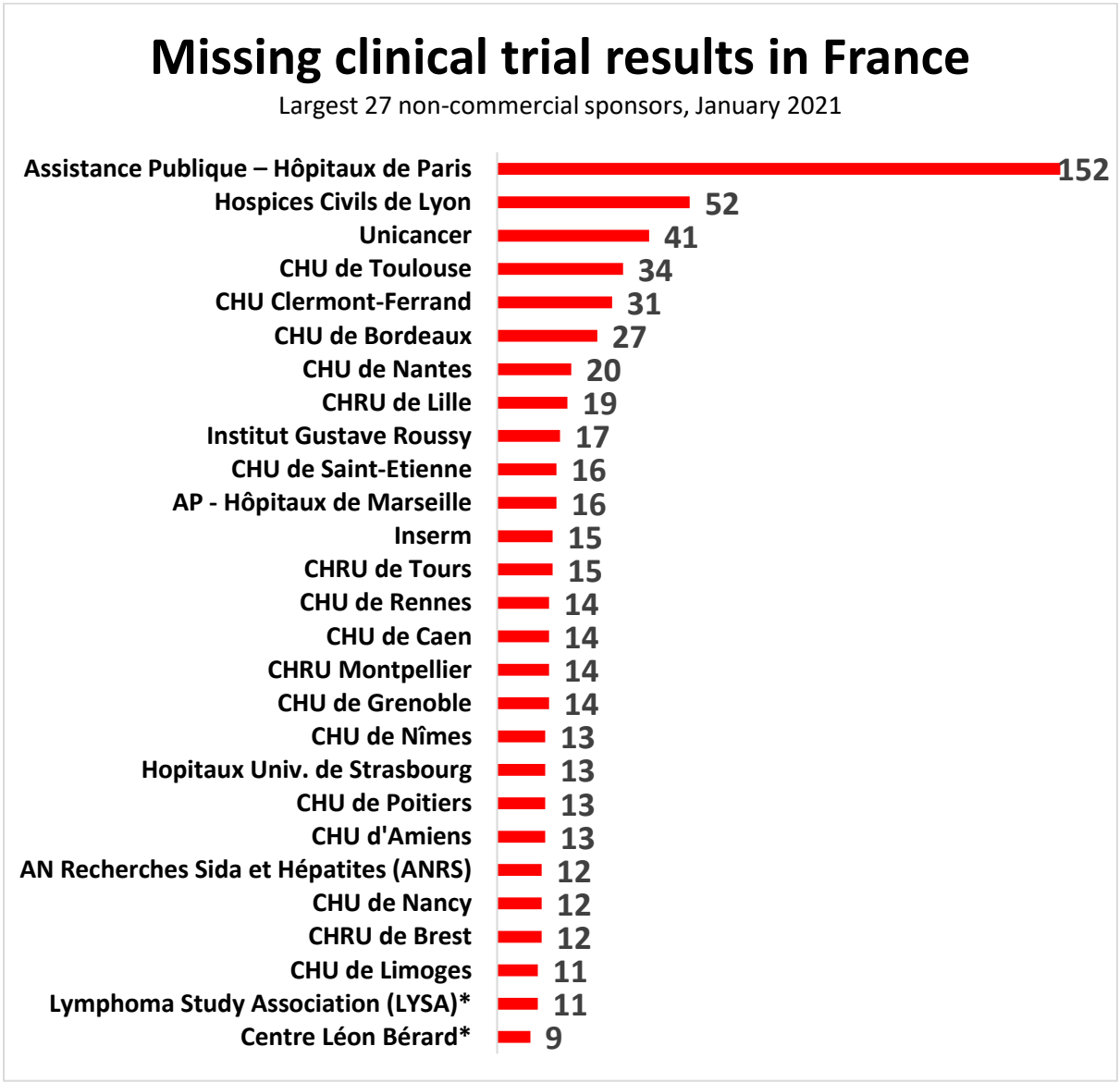
Even this 7% reporting figure is an over-estimate because most registry data on these sponsors' trials is inconsistent or out of date. For example, it is implausible that only 159/1,324 non-commercial trials (12%) have been completed more than a year ago, compared to 367/1096 of industry trials (33%). To provide a more accurate picture, the next section provides an estimate of the true number of missing trial results for each non-commercial sponsor.

[2] Sanofi Pasteur MSD was a joint venture between two companies. As a separate legal entity, it was permitted to act as the legal sponsor of clinical trials. The joint venture was discontinued in 2016.

3 ESTIMATED NUMBER OF MISSING CLINICAL TRIAL RESULTS

The 27 largest non-commercial sponsors in France have failed to report an estimated 630 clinical trial results in violation of European Union transparency rules.

The largest such sponsor, ***Assistance Publique – Hôpitaux*** de Paris, has failed to make public the results of an estimated 152 drug trials. ***Hospices Civils de Lyon*** is the second-worst offender (52 results estimated missing), followed by ***Unicancer*** (41 results). The chart below provides estimates for each of the 27 sponsors. Only two non-profit sponsors, ***Lymphoma Study Association (LYSA)*** and the ***Centre Léon Bérard***, have a strong disclosure record; both have committed to making all of their trial results public soon.[3] For all other sponsors, estimates closely correlate with their overall portfolio size.



** Estimates re-calculated and adjusted downwards based on manual review of registry data*

[3] The estimates of trials missing results for these two sponsors were re-calculated and adjusted downwards based on a manual review of registry data. Please see the methodology section for further details. Shortly before publication of this report, ***LYSA*** provided TranspariMED with a detailed breakdown of its portfolio suggesting that only two due LYSA trials were missing results. To maintain methodological consistency, the chart on this page reflects the original estimate of eleven missing LYSA trial results. Both ***LYSA*** and ***Centre Léon Bérard*** have assured TranspariMED that they are now actively working towards a 100% reporting rate. TranspariMED welcomes their commitment to excellence in clinical trial transparency.

4 DATA QUALITY PROBLEMS

Going forward, TranspariMED and MelanomeFrance will produce regular updates of this report to track French trial sponsors' progress over time.

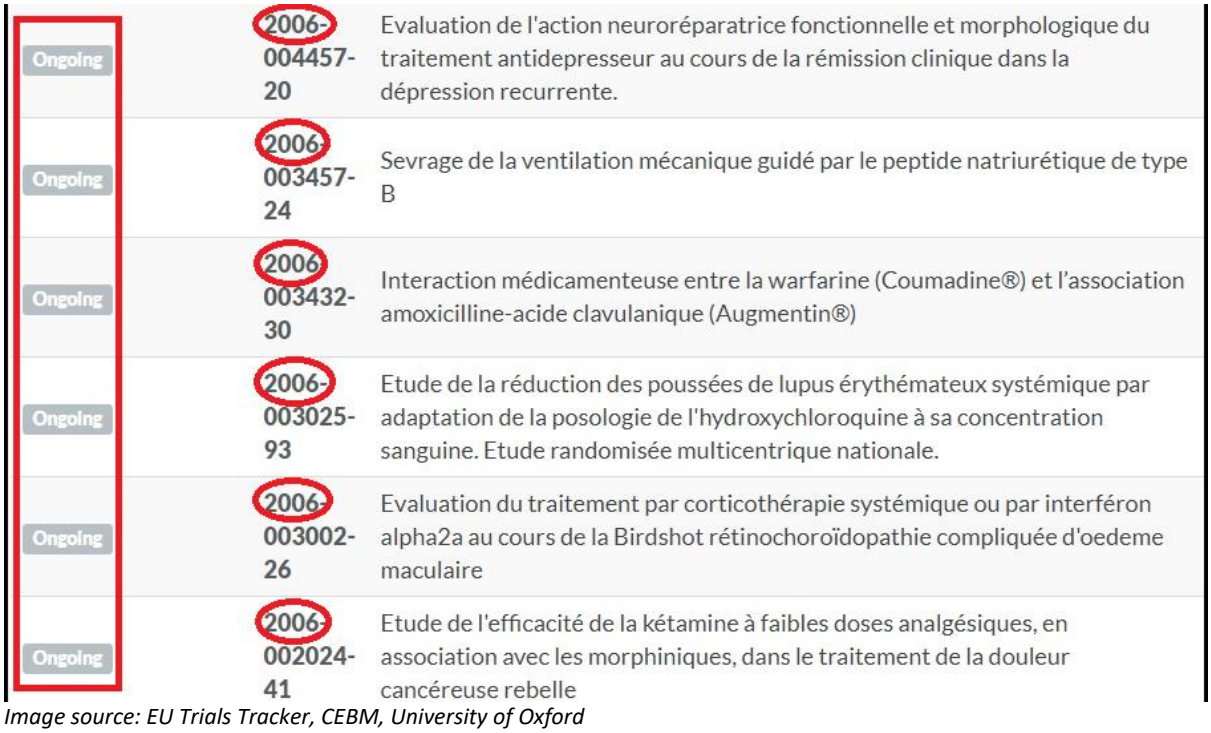
Recurring quality problems with French sponsors' entries on the European Clinical Trial Register include incomplete, incorrect, inconsistent and out-of-date data. Sponsors' weak data management undermines the utility of the European trial registry for patients, doctors and researchers.

This report provides *estimates* of French non-commercial sponsors' missing trial results because these sponsors have failed to ensure that the data on their trials in the registry is accurate and up to date. (French commercial sponsors tend to manage their data somewhat better, but also not perfectly.)

This section discusses the trial portfolio of the largest French non-commercial trial sponsor, ***Assistance Publique – Hôpitaux de Paris (AP-HP)*** to illustrate the nature and scale of these problems. However, all French sponsors' portfolios have similar data quality problems.

Frequently, trials that have been completed long ago remain falsely listed as 'ongoing' on the registry because their sponsors have failed to ensure that the registry entry is updated. For example, AP-HP's portfolio consists of 307 drug trials. Of those, only 28 trials are marked as 'completed' and have a completion date.

A further 233 AP-HP trials are listed as still 'ongoing', but as the screenshot below shows, many of those trials were started over decade ago and have almost certainly been completed long ago.



Ongoing	2006-004457-20	Evaluation de l'action neuroréparatrice fonctionnelle et morphologique du traitement antidepresseur au cours de la rémission clinique dans la dépression recurrente.
Ongoing	2006-003457-24	Sevrage de la ventilation mécanique guidé par le peptide natriurétique de type B
Ongoing	2006-003432-30	Interaction médicamenteuse entre la warfarine (Coumadine®) et l'association amoxicilline-acide clavulanique (Augmentin®)
Ongoing	2006-003025-93	Etude de la réduction des poussées de lupus érythémateux systémique par adaptation de la posologie de l'hydroxychloroquine à sa concentration sanguine. Etude randomisée multicentrique nationale.
Ongoing	2006-003002-26	Evaluation du traitement par corticothérapie systémique ou par interféron alpha2a au cours de la Birdshot rétinochoroïdopathie compliquée d'oedeme maculaire
Ongoing	2006-002024-41	Etude de l'efficacité de la kétamine à faibles doses analgésiques, en association avec les morphiniques, dans le traitement de la douleur cancéreuse rebelle

Image source: EU Trials Tracker, CEBM, University of Oxford

The remaining 46 AP-HP drug trials have inconsistent completion data. This includes 5 trials that remain listed as 'ongoing' even though they also have a completion date, as the example of the paediatric trial below shows.

Status	Trial ID	Title	Completion date
Listed as ongoing, but also has a completion date	2009-012203-26	Efficacy and safety of inhaled Budesonide in Very Preterm Infants at Risk for Bronchopulmonary Dysplasia.	2016-07-31
Completed, but no date Terminated	2008-004949-28	Traitement par le monoxyde d'azote inhalé (NO) du syndrome thoracique aigu (STA) chez l'enfant drépanocytaire : Essai randomisé, double aveugle, contre placebo, preuve de concept	
Completed, but no date	2008-003982-21	Etude des transporteurs de la dopamine et de la sérotonine en imagerie TEMP utilisant les radiopharmaceutiques 123I-FP-CIT (datscan) and 123 I-ADAM dans la sclérose latérale amyotrophique et dans	

Image source: EU Trials Tracker, CEBM, University of Oxford

Impact on patients and medical progress

These data quality issues negatively impact patients and slow down scientific progress:

- Health technology assessment agencies, horizon scanners, systematic reviewers and medical researchers cannot reliably determine whether a trial is still ongoing or has been prematurely ended, terminated, or completed. This makes it difficult to gain an overview of the complete scientific evidence base on a medicine, leading to needless duplications of research efforts.
- Clinicians, patient groups and patients cannot reliably determine which trials may currently be recruiting patients, making enrolment more difficult for patients and recruitment more difficult for sponsors. This drives up the cost and slows down the pace of medical research.
- Compliance with EU reporting rules is undermined because it is impossible to determine exactly which trials have been completed and are obliged to make their results public.

Role and responsibility of Agence Nationale de Sécurité du Médicament (ANSM)

The problems flagged above may originate with trial sponsors, with ANSM, or with both. When a trial is completed, the sponsor should send an 'End of Trial Notification' to ANSM; ANSM should then update the status of the trial on the registry and also enter the completion date (sponsors cannot do these steps themselves). If either party fails to perform its role, the registry does not get updated.

It is impossible to discern from registry records whether French sponsors have sent some or all of the required notifications to ANSM. ANSM's press office did not respond to an invitation by TranspariMED to provide a statement for inclusion in this report.

As the French national regulator, ANSM is ultimately responsible for safeguarding the quality of French trial data on the European register. ANSM should engage in a dialogue with trial sponsors and work together with them to improve data quality and ensure that data on the register are consistent and accurate.

5 COVID DRUG TRIALS IN FRANCE

Currently, 15 out of 20 French institutions running Covid drug trials[4] are in violation of transparency rules. Only one of Covid trial sponsor has a strong compliance record. The remaining four sponsors have no compliance track record as none of their past trials are due to report results yet.

Overall, the 20 French sponsors are currently responsible for 32 Covid drug trials involving 14,400 patients.[5]

The table below lists all 20 trial sponsors in alphabetical order, and notes whether they are currently compliant with European transparency rules. All Covid trials listed are required by European Union rules to make their results public within one year of trial completion. More details on each trial can be found by searching for the trial number in Google.

SPONSOR	Compliant?	Trial number	Patients
AB Science	**NO**	EUCTR2020-001635-27-FR	200
Abivax	**NO**	EUCTR2020-001673-75-FR	1034
Assistance Publique – Hôpitaux de Marseille	**NO**	EUCTR2020-001301-23-FR	584
		EUCTR2020-001686-36-FR	116
		EUCTR2020-001754-21-FR	150
		EUCTR2020-001766-11-FR	90
Assistance Publique – Hôpitaux de Paris	**NO**	EUCTR2020-001301-23-FR	584
		EUCTR2020-001381-11-FR	554
		EUCTR2020-001457-43-FR	550
		EUCTR2020-001678-31-FR	1120
		EUCTR2020-001700-42-FR	230
		EUCTR2020-001909-22-FR	212
Biophytis	**n/a***	EUCTR2020-001498-63-FR	465
Centre Hospitalier de Versailles	**NO**	EUCTR2020-001598-66-FR	20
		EUCTR2020-001768-27-FR	39
CHRU Montpellier	**NO**	EUCTR2020-001406-27-FR	120
CHU d'Angers	**NO**	EUCTR2020-001271-33-FR	1300
CHU de Bordeaux	**NO**	EUCTR2020-001435-27-FR	1057
CHU de Caen	**NO**	EUCTR2020-001867-94-FR	180
CHU de Nancy	**NO**	EUCTR2020-001709-21-FR	550
CHU de Nantes	**NO**	EUCTR2020-003689-37-FR	30
		EUCTR2020-002574-27-FR	368
CHU de Saint Etienne	**NO**	EUCTR2020-001281-11-FR	50
		EUCTR2020-001823-15-FR	200
CHU de Tours	**NO**	EUCTR2020-001734-36-FR	240
Fondation Méditerranée Infection	**n/a***	EUCTR2020-000890-25-FR	25
Groupe Hospitalier Paris Saint-Joseph	**n/a***	EUCTR2020-001333-13-FR	122
		EUCTR2020-001723-13-FR	640
Inotrem	**NO**	EUCTR2020-001504-42-FR	60
Inserm	**NO**	EUCTR2020-000936-23-FR	3100
L'Hôpital Fondation Adolphe de Rothschild	**n/a***	EUCTR2020-001492-33-FR	100
Sanofi**	**YES****	EUCTR2020-001270-29-FR	350

** Note: Sponsor does not have any compliance record as none of its past trials are due to report results yet.*

** Sanofi has reported the results of 178/179 of its verifiably due trials (>99% compliance).

[4] French sponsors are running additional Covid trials that do not fall under EU reporting rules. Those trials fall outside the scope of this report (see methodology section). The complete list of all Covid trials is available for download on the Covid-19 TrialsTracker website.

[5] All trials listed aim to recruit French patients; a minority of trials will also recruit patients abroad. The figures in the table are global recruitment targets. Trials may end up recruiting more or less patients than was originally planned.

COVID TRIAL CASE STUDY: SANOFI'S HYDROXYCHLOROQUINE TRIAL

The case of the only French Covid trial run by a sponsor with a good transparency record, ***Sanofi***, illustrates how strong registry management can contribute to accelerating medical progress and informing treatment choices.

In this trial of the drug hydroxychloroquine, Sanofi originally aimed to recruit 350 patients. It started recruiting patients in April 2020, but decided to prematurely end the trial in June 2020 after evidence from other trials suggested that the drug was unlikely to help patients with Covid. At that point, Sanofi had only recruited and randomised 14 patients.

Publishing the results of this trial exclusively in a medical journal would have made little or no contribution to scientific progress or patient care. It typically takes 2-3 years to get a trial result published in a journal, so the results of this Covid trial would not have been publicly accessible in a journal until 2022 or 2023, (hopefully) long after the pandemic has subsided. Furthermore, most journals would not be interested in publishing the results of a trial with only 14 patients that investigated a treatment option that is currently widely regarded as unpromising.

Sanofi rapidly uploaded the trial's results onto the European registry, long before the 12 month regulatory deadline had expired. Thanks to Sanofi's strong registry management, systematic reviewers and meta-analysts can now pool the data from this small trial with data from other trials to get a more complete picture of the benefits and harms of hydroxychloroquine.

The track record of most other French sponsors suggests that they would have failed to update the trial's status on the registry, making it impossible for outsiders to determine whether the trial was still ongoing or had ended. The uncertainty created by such weak data management prevents funding agencies and scientists from getting reliable information on who is currently researching which potential treatments, leading to costly duplication and avoidable gaps in research efforts.

In addition, based on their past performance, most other French sponsors would not have uploaded the trial's results onto the registry after the trial had ended. Because no prominent journal would be interested in publishing these results of this small trial, academic researchers would have had no incentive to seek publication. Very likely, this trial's results would never have been made public at all, in any form.

Many other Covid-19 trials in France (and worldwide) are likely to be discontinued or terminated early, and are therefore at high risk of becoming research waste.

Globally, an estimated $85 billion in medical research funding are wasted every year because research results are not made public, often due to reasons similar to those discussed above. Only strong and consistent registry management by sponsoring institutions can ensure that every single clinical trial result is rapidly made public.

Unless ***Agence Nationale de Sécurité du Médicament (ANSM)*** rapidly takes action and contacts French trial sponsors, many trials involving French Covid patients – including trials funded with public money – will end up as research waste and make no contribution to scientific progress, to improving patient care, or to ending the pandemic.

5 WHY THIS MATTERS

Relevance to public health and clinical practice

Failure to report clinical trial results is not a victimless crime. A 2017 report by Transparency International and Cochrane documents that a failure to fully report trial results has substantial negative consequences:

- Patients are harmed
- Public health agencies cannot make informed decisions
- Public health funds are wasted
- Medical progress is slowed down

Legal and regulatory framework

European Union rules adopted in July 2014 require each and every clinical trial registered on the EU Clinical Trials Registry to post summary results to the registry within 12 months of trial completion (6 months for paediatric trials). These rules also apply to trials completed before 2014 and apply irrespective of whether a trial's outcomes have been published in the academic literature.

Thus, all of the clinical trials identified in this report as missing summary results are in violation of EU transparency rules that were designed to protect the interests of patients and taxpayers. Once the EU Clinical Trial Regulation comes into force in late 2021, national medicines regulators will have the power to fine institutions for not uploading trial results to the registry.

Concerns about research waste

Unreported trials contribute nothing to progress in science and public health and are therefore costly research waste. In the past, unreported clinical trial results have caused public health losses amounting to billions of Euros and have led to the deaths of countless patients. For this reason, the Declaration of Helsinki has made reporting the results of every clinical trial a universal ethical obligation for all medical researchers worldwide.

While not all trials lacking results on the European trial registry are completely unreported, the best available evidence suggests that around half of all trials missing results on the registry have also not reported their results in academic journals. Thus, many trials run by the sponsors covered in this report are in acute danger of becoming research waste unless their results are made public soon.

Pharmaceutical companies, universities and hospitals should review their clinical trial portfolios across the European registry, the American registry ClinicalTrials.gov, and other WHO primary trial registries, identify those trials that have remained completely unreported, and ensure that their results are made public as soon as possible.

Global best practices

WHO standards require every sponsor of an interventional trial to post its results on every public registry where it was registered within 12 months of its primary completion date. Importantly, the WHO has explicitly stated that publishing trial results in the academic literature is ***not*** an acceptable substitute for uploading trial results onto public registries.

Best practices jointly set out by Cochrane and Transparency International also state that 'summary results for all clinical trials should be posted on the registries where they were originally registered

within 12 months of study completion'. The two health integrity groups note that retrospectively posting the results of all past trials to registries 'would improve healthcare delivery and government agencies' decision-making on resource allocations, as well as saving billions of dollars' worth of medical research from being lost forever'.

Similarly, the trial reporting benchmark set out by the AllTrials campaign states that '[a] summary of results (…) should be posted where a trial was registered within one year of completion of a trial'.

Why is posting trial results to registries so important?

There are good reasons why global best practices require posting results of ***all*** trials ***onto registries***:

- Posting results onto registries accelerates medical progress because the 12-month timeline permits far more rapid results sharing than the slow academic publication process allows.
- Posting results to registries minimises the risk of a trial never having its results reported and becoming research waste, which can happen when a principal investigator dies or leaves their post during the prolonged process of submitting an academic paper to a succession of medical journals.
- Research shows that trial results posted on registries typically give a more comprehensive and accurate picture of patient-relevant trial outcomes than corresponding journal articles do.
- Results posted on registries are easier to locate and are open access.
- Registry reporting facilitates the comparison of trial outcomes with a trial's originally stated aims and, thus, discourages harmful research malpractices such as HARKing, p-hacking and the 'silent' suppression, addition or switching of the selected outcomes.

Please see the report by Cochrane and Transparency International for further details and links to the relevant literature.

Uploading results to trial registries typically precedes publication in academic journals

There is no recorded case, ever, in which a manuscript was rejected by a journal because the trial results had already been uploaded to a trial registry.

Academic journals will accept articles reporting a trial's outcomes even if that trial's outcomes have already been made public in a trial registry. The International Committee of Medical Journal Editors has explicitly stated that the posting of summary results to trial registries is not considered prior publication by academic journals. Thus, because results reporting on registries is typically faster than academic publication, making trial results public on registries before they are published in an academic journal is becoming the new norm in scientific communications.

ANNEX 1: DATA TABLE

The table below displays the data for non-commercial sponsors cites in this report. (Data for commercial sponsors can be found in the report itself.)
All data were extracted from the EU Trials Tracker on 04 February 2021, and reflect publicly visible registry data as of 31 January 2021.

Sponsor	**Trials total**	Results due*	With results*	No results*	**Results missing****	**Hyperlink** (link to the sponsor's EU Trials Tracker data)
Assistance Publique – Hôpitaux de Paris	**307**	28	1	27	**152**	http://eu.trialstracker.net/sponsor/hospitals-of-paris-ap-hp
Hospices Civils de Lyon	**104**	14	0	14	**52**	http://eu.trialstracker.net/sponsor/hospices-civils-de-lyon
Unicancer	**82**	5	0	5	**41**	http://eu.trialstracker.net/sponsor/unicancer
CHU de Toulouse	**69**	12	0	12	**34**	http://eu.trialstracker.net/sponsor/chu-de-toulouse
CHU Clermont-Ferrand	**62**	10	0	10	**31**	http://eu.trialstracker.net/sponsor/chu-clermont-ferrand
CHU de Bordeaux	**54**	9	0	9	**27**	http://eu.trialstracker.net/sponsor/chu-de-bordeaux
Lymphoma Study Association (LYSA)* **	**49**	8	5	3	**11**	http://eu.trialstracker.net/sponsor/the-lymphoma-study-association-lysa
CHU de Nantes	**45**	8	2	6	**20**	http://eu.trialstracker.net/sponsor/chu-de-nantes
CHRU de Lille	**39**	3	0	3	**19**	http://eu.trialstracker.net/sponsor/chru-de-lille
Institut Gustave Roussy	**35**	2	0	2	**17**	http://eu.trialstracker.net/sponsor/institut-gustave-roussy
AP - Hôpitaux de Marseille	**33**	3	0	3	**16**	http://eu.trialstracker.net/sponsor/hospitals-of-marseille
CHU de Saint-Etienne	**32**	1	0	1	**16**	http://eu.trialstracker.net/sponsor/chu-de-saint-etienne
Centre Léon Bérard* **	**31**	6	3	3	**9**	http://eu.trialstracker.net/sponsor/centre-leon-berard
CHRU de Tours	**31**	3	0	3	**15**	http://eu.trialstracker.net/sponsor/chru-de-tours
Inserm	**31**	3	0	3	**15**	http://eu.trialstracker.net/sponsor/inserm
CHU de Grenoble	**29**	6	0	6	**14**	http://eu.trialstracker.net/sponsor/chu-de-grenoble
CHRU Montpellier	**29**	5	0	5	**14**	http://eu.trialstracker.net/sponsor/chru-montpellier
CHU de Caen	**29**	5	0	5	**14**	http://eu.trialstracker.net/sponsor/chu-de-caen
CHU de Rennes	**28**	3	0	3	**14**	http://eu.trialstracker.net/sponsor/chu-de-rennes
CHU d'Amiens	**27**	1	0	1	**13**	http://eu.trialstracker.net/sponsor/chu-damiens
CHU de Poitiers	**27**	2	0	2	**13**	http://eu.trialstracker.net/sponsor/chu-de-poitiers
Hopitaux Univ. de Strasbourg	**27**	8	0	8	**13**	http://eu.trialstracker.net/sponsor/hopitaux-universitaires-de-strasbourg
CHU de Nîmes	**27**	4	0	4	**13**	http://eu.trialstracker.net/sponsor/chu-de-nimes
CHRU de Brest	**25**	4	0	4	**12**	http://eu.trialstracker.net/sponsor/chru-de-brest
CHU de Nancy	**25**	1	0	1	**12**	http://eu.trialstracker.net/sponsor/chu-de-nancy
AN Recherches Sida et Hépatites (ANRS)	**24**	0	0	0	**12**	http://eu.trialstracker.net/sponsor/agence-nationale-de-recherches-sur-le-
CHU de Limoges	**23**	5	0	5	**11**	http://eu.trialstracker.net/sponsor/chu-de-limoges
TOTAL	**1324**	**159**	**11**	**148**	**630**	

*Notes: *Based on registry data; **Estimated true number of due trials missing results; ***Portfolio reviewed manually, see also footnote on page 5 for LYSA*

ANNEX 2: METHODOLOGY AND LIMITATIONS

Authorship

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Data extraction: Nicholas DeVito (EBM Data Lab, University of Oxford)

The author would like to thank Nicholas DeVito for volunteering his time and expertise for extracting the data used for cohort selection. EBM Data Lab as an institution was not involved in developing this report. Any errors in this report are exclusively the responsibility of TranspariMED. The author does not have any potential financial conflict of interest. Neither TranspariMED nor the author have ever received funding from the pharmaceutical industry.

Methodology

Data extraction

The EU Clinical Trial Register (EUCTR) was scraped and processed using EU TrialsTracker code and the standard methodology to determine the reporting status of each trial. As part of the process, free-text sponsor names are normalised for display on the website. Alongside the standard EUCTR scraper, a second scraper was run to obtain detailed sponsor info from section B of each EUCTR country level protocol (specifically the sponsor name, country, and sponsor status). This detailed sponsor information was then combined with the processed EU TrialsTracker data, and normalisation data, to extract all trials with a French sponsor.

The data in this report reflect data publicly available on EUCTR as of 31 January 2021.

The codes used are available on Github:

- EU Trials Tracker code and data
- EUCTR Sponsor section scraper
- The code for generating the dataset

Cohort selection

The main cohort for this study consists of 33 clinical trial sponsors headquartered in France that had sponsored 23 or more clinical trials on EUCTR as of 31 January 2021.

The full data set listed 39 sponsors that had run 23 or more trials. Based on a manual search of sponsor websites, 6 sponsors were removed because their headquarters are located outside France: Boehringer Ingelheim, Galderma, Merck Sharp & Dohme (MSD), Novartis, Pfizer, and Roche.

Assigning trials to sponsors

This report reflects the sponsor portfolios adopted by the EU Trials Tracker, with a few exceptions:

Sanofi. A Tracker search returned three entries for Sanofi:

- Sanofi S.A. (680 trials)
- Sanofi (2 trials)
- Sanofi Pasteur MSD (29 trials)

The data for Sanofi S.A. and Sanofi are aggregated in this report under the name "Sanofi".

Sanofi Pasteur MSD is considered a separate sponsor because it was a stand-alone joint venture until it was discontinued in 2016. TranspariMED is unclear which entity currently has the regulatory obligation to manage Sanofi Pasteur MSD's legacy trial portfolio. Results are outstanding for only one trial in the portfolio.

Bioprojet. A Tracker search returned two entries for "Bioprojet":

- Bioprojet (17 trials)
- Bioprojet Pharma (5 trials)

Their data are aggregated in this report under the name "Bioprojet".

Measuring verifiable sponsor performance

Data on the clinical trial performance of each of the sponsors was manually extracted from the EU Trials Tracker on 04 February 2021.

The tracker data reflected trial results that were publicly available on EUCTR as of 31 January 2021. Due to delays by the European Medicines Agency in making public trial results submitted by sponsors, the tracker data might not include all trial results that were uploaded by sponsors during the preceding month. Thus, the data in this report reflect sponsors' trial reporting performance as of early January 2021.

The EU Trials Tracker was built by the EBM Data Lab, University of Oxford, and in 2018 its methodology was published in the BMJ, a peer reviewed journal. The tracker is based exclusively on data that are publicly available on the EUCTR; the tracker is updated on a monthly basis. To the best of the author's knowledge, to date no instances of a trial incorrectly flagged as being due and missing results by the EU Trials Tracker based on registry records have been detected. The EU Trials Tracker individually lists every trial flagged as overdue, and includes a link back to the original registry entry for every trial. Thus, all data in this report are externally replicable.

Estimating the true number of trials missing results

Because the national regulator and trial sponsors in France have collectively failed to ensure that data on the European trial register is accurate and up to date, many completed trials are falsely marked as 'ongoing' or lack a completion date. This makes it impossible to precisely determine the number of trials missing results.

Estimates on the number of trials missing results were calculated based on the assumption that 50% of each institution's trials were completed more than a year ago and are therefore currently due to upload their results. TranspariMED divided the total number of trials per institution in half to arrive at an estimate of its due trials, and then subtracted the number of trials listed as both 'due' and 'reported' by the EU Trials Tracker. The resulting numbers were rounded down to the next integer if applicable.

The 50% assumption is based on the fact that the European register captures trials that began as early as 2004, and trials usually only run for a few years. Therefore, the register contains many trials that have been completed. In the trial portfolios of major sponsors in other European countries for which more reliable data are available, around half of all trials appear due to report results.[6]

[6] For example, data on Imperial College London's trial portfolio can be considered reasonably reliable because the university has reported over 97% of its verifiably due trials, has nearly no trials with inconsistent completion data, and has few very old

Exceptions: Following a manual review of their trial portfolios, the estimated number of missing trial results was re-calculated and adjusted downwards for two non-commercial sponsors, ***Lymphoma Study Association (LYSA)*** and the ***Centre Léon Bérard***. Both sponsors have reported results for several trials that are not counted as fully reported by the Tracker. [7] (The Tracker only counts trials as fully reported if they have results *and* are marked as completed *and* have a completion date.)

- Lymphoma Study Association (LYSA): The Tracker counts only 5 LYSA trials as fully reported. LYSA has additionally reported the results for 6 trials that are falsely marked as 'ongoing', and for 2 trials with an 'inconsistent' completion status. Thus, the estimate for unreported LYSA trials was re-calculated based on a total of 13 trials having results available.
- Centre Léon Bérard (CLB): The Tracker counts only 3 CLB trials as fully reported, but 2 false 'ongoing' and one 'inconsistent data' trial also have results. The CLB estimate was re-calculated based on a total of 6 trials having results. All CLB results were uploaded during 2019-2020, indicating that CLB may be making efforts to clear its backlog of unreported trials.

Shortly before publication of this report, both LYSA and Centre Léon Bérard contacted TranspariMED with a complete list of their respective drug trials. Please see the footnote on page 5 for details.

Data on Covid-19 drug trials

A list of all registered Covid clinical trials worldwide was extracted from the Covid-19 TrialsTracker dataset by Nicholas DeVito. The author manually and progressively excluded from the list trials that (1) were not registered on EUCTR, (2) did not have a trial location in France, and (3) were not sponsored by an entity headquartered in France. The final cohort includes all Covid clinical trials that had been registered on EUCTR and were publicly visible there as of 11 November 2020.

Limitations

Reliance on estimates for the true number of trials missing results

Many French trials are almost certainly falsely marked as 'ongoing' in the registry even though they were in fact completed long ago. However, the exact number of such trials is impossible to determine based on registry data alone, making it necessary to generate an estimate of the true number of due trials missing results (see above).

Undercounting of results posted

Due to delays by the European Medicines Agency in making public trial results submitted by sponsors, trial results that were uploaded during the second half of January 2021 may not have been captured by the EU Trials Tracker. In consequence, some trials whose results were only recently made public on EUCTR may have been counted as unreported. In TranspariMED's experience, the number of such trials is likely to be very low in a cohort this size. In addition, the Tracker lists trials with results that are not marked as completed and/or have no completion date in the protocol as having "inconsistent data"; such trials are not counted as 'reported' by the Tracker or in this report. The number of such trials in non-commercial sponsors' portfolios is low.

trials that are still marked as 'ongoing'. Out of Imperial's 139 trials total, 76 trials (55%) are marked as being due to report results.

[7] Similar adjustments were not made for other non-commercial sponsors because very few of none of their false 'ongoing' and 'inconsistent data' trials have results available. For example, AP-HP has 2 only such trials in its entire portfolio of 307 drug trials.

Assigning trials to sponsors

Sponsor names are not normalised in EUCTR, so the EU Trials Tracker team had to manually normalise all sponsor names. In some cases, the legal responsibility for reporting results was difficult to establish, and some sponsoring institutions may have been incorrectly aggregated or disaggregated.

Please note that the EU Trials Tracker was developed and is being maintained by a team at the University of Oxford, and not by TranspariMED.

Note: If sponsors discover that trials have been incorrectly allocated to them, or would like multiple portfolios to be merged, they can contact the EU Trials Tracker team, which will review their claim and, if appropriate, make adjustments. Such changes will become publicly visible at the beginning of the following month, after the Tracker has undergone its regular monthly update.

Trials not listed on the EU Clinical Trial Register

The data in this report exclusively cover clinical trials that were registered on the EU Clinical Trial Register. Under EU rules, all clinical trials of investigational medicinal products (CTIMPs) conducted in the European Union ***must*** be registered on the EU Clinical Trial Register, and sponsors ***must*** post the results of those trials onto the register within 12 months of trial completion.

Non-drug trials, including trials of medical devices (e.g. pacemakers or artificial hips) and non-drug treatments (e.g. surgery or physiotherapy), ***cannot*** be registered on the EU Clinical Trial Register and are thus registered on other trial registries. Assessing sponsors' reporting performance for these non-drug trials is beyond the scope of this report.

However, non-drugs trials can be of even greater medical importance than drug trials. Sponsors are required to make their results public (in some form) under global ethics rules, and according to WHO best practices, sponsors should make their results public on a trial registry within 12 months of trial completion. However, regulatory oversight of non-drug trials is currently weak across Europe.

The lack of European transparency rules for non-drug trials makes it important for France to develop a national clinical trial transparency strategy to ensure that *all* clinical trials involving French patients are registered and their results made public.[8]

[8] The UK has already developed such a national strategy, see here: https://www.transparimed.org/single-post/2020/09/14/uk-clinical-trial-registration-reporting