Institution: University of Oxford		
Unit of Assessment: 2 – Public Health, Health Services and Primary Care		
Title of case study: Enhancing clinical trial transparency and reporting		
Period when the underpinning research was undertaken: 2009 – 2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Carl Heneghan	Professor of Evidence-Based Medicine	Oct 2005 – present
Kamal R. Mahtani	Associate Professor	Mar 2012 – present
Ben Goldacre	Senior Clinical Research Fellow	Mar 2015 - present
Seb Bacon	Chief Technology Officer	July 2019 – present
Period when the claimed impact occurred: Aug 2013 – Dec 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

Non-reporting and mis-reporting of clinical trial data distorts the evidence base for optimal clinical practice. Researchers at the at the University of Oxford, working in the Centre for Evidence Based Medicine (CEBM), developed novel methods to interrogate clinical trial data and audit ongoing trials. Using these new methods, the Oxford CEBM published research studies that resulted in worldwide changes in the recommendations for the use of neuraminidase inhibitors for influenza. Based on these results and the challenges overcome in achieving them, Oxford researchers went on to develop TrialsTracker, a live data science tool for automated assessment of clinical trials reporting. Policies to increase clinical trial data transparency have been implemented worldwide, and compliance of clinical trials with both EU and FDAAA reporting laws have increased as a result of TrialsTracker.

2. Underpinning research

In April 2009, the WHO declared a public health emergency of international concern in response to the threat of a pandemic of swine influenza A(H1N1). In preparation for the pandemic, the WHO advised member states to stockpile antiviral neuraminidase inhibitors (NIs). These included inhaled zanamivir and oral oseltamivir ("Tamiflu").

In 2009, the Australian and UK governments commissioned an update of the longstanding Cochrane review on neuraminidase inhibitors (A047). Heneghan led an international collaboration of researchers to evaluate the benefit to harm profile of NIs and uncovered unresolved discrepancies in the data presented in published trial reports and substantial publication bias. Eight of the 10 trials on NIs had never been published and complete datasets were unavailable. In 2010, the University of Oxford team, led by Heneghan as Chief Investigator, concerned that many clinical trials were not being published, began to update this Cochrane systematic review. They elected not to use data from journal articles, and instead sought, catalogued, and synthesised only pre-licensing regulatory data. Supported by the British Medical Journal (BMJ) and a protracted media campaign, the team obtained and analysed data from the European Medicines Agency and other regulators in the UK, USA, and Japan, and engaged with industry to obtain unpublished data. In excess of 160,000 pages of regulatory data were obtained, mostly in the form of 107 unpublished clinical study reports (CSRs) from 46 trials (20 oseltamivir and 26 zanamivir).

The Cochrane review was the first entry in the Cochrane Library to use only unpublished regulatory documentation. Since at that time there were no professional standards, guidelines, or training on how to incorporate these detailed reports into a systematic review, in the process of preparing these syntheses the researchers had developed new techniques and processes for conducting the analysis, and published those in 2018 [1].

The team published their results on NIs as three systematic reviews in April 2014, one in the Cochrane Library (Cochrane A159) [2] and a pair in the BMJ [3a,3b], showing minimal benefit of antivirals for the treatment of influenza and new evidence of the potential harms of these drugs.

Non-reporting of clinical trials can distort the evidence-base for clinical practice, breaches researchers' ethical obligations to participants, and represents an important source of research waste. To automatically identify and audit all trials covered by EU and US legislation, in 2016, Goldacre developed a live data science tool, TrialsTracker, showing the promise of automated assessment of clinical trials reporting and published its methods [4]. EU Guidelines requiring the reporting of all registered trials on the EU Clinical Trials Register following completion came into full effect in late 2016. Simultaneously the US Department of Health and Human Services finalised federal rulemaking that clarified many aspects of the FDA Amendments Act 2007 which requires certain trials to report directly to ClinicalTrials.gov. However, neither the US nor EU regulators showed any indication of which trials were due and which were not fulfilling their reporting obligations. The development by the DataLab team at the University of Oxford of the FDAAA TrialsTracker in February 2018 [5] and the EU TrialsTracker [6] in September 2018, and their application to those sets of trials, have expanded the automated tracking work and highlighted substantial gaps in compliance with the law, especially among small and non-industry funders.

3. References to the research (University of Oxford staff in bold and Oxford students in italics)

1 Jefferson T, Doshi P, Boutron I, Golder S, **Heneghan C**, Hodkinson A, Jones M, Lefebvre C and Stewart I. When to include clinical study reports and regulatory documents in systematic review *BMJ Evidence-Based Medicine* 2018; **23:**210-217. DOI: 10.1136/bmjebm-2018-110963

2 Jefferson T, Jones MA, Doshi P, Del Mar CB, Hama R, Thompson MJ, **Spencer EA**, **Onakpoya IJ, Mahtani KR**, **Nunan D, Howick J** and **Heneghan CJ** (2014). Neuraminidase inhibitors for preventing and treating influenza in adults and children. *Cochrane Library Review* A159. DOI: 10.1002/14651858.CD008965.pub4 339 citations (First version published January 2012, updated with additional data and feedback 10 April 2014)

3(a) **Heneghan CJ**, **Onakpoya I**, Thompson M, **Spencer E**, Jones M and Jefferson T. Zanamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments. *BMJ* 2014; **348**:g2547–g2547. DOI: 10.1136/bmj.g2547 62 citations

3(b) Jefferson T, Jones M, Doshi P, **Spencer E, Onakpoya I, Heneghan, C**. Oseltamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments. *BMJ* 2014;**348**:g2545. DOI: 10.1136/bmj.g2545. 266 citations

4 **Powell-Smith A** and **Goldacre B**. The TrialsTracker: Automated ongoing monitoring of failure to share clinical trial results by all major companies and research institutions. F1000Res 2016;**5**:2629 DOI: 10.12688/f1000research.10010.1. 18 citations

5 *DeVito NJ*, **Bacon S** and **Goldacre B** Compliance with legal requirement to report clinical trial results on ClinicalTrials.gov: a cohort study. *The Lancet* 2020 Volume 395, Issue 10221, 361 – 369 DOI: 10.1016/S0140-6736(19)33220-9. 21 citations

6 **Goldacre B,** *DeVito NJ*, **Heneghan C, Irving F,** Bacon S, *Fleminger J,* **Curtis H**. Compliance with requirement to report results on the EU Clinical Trials Register: cohort study and web resource *BMJ* 2018; 362 :k3218 DOI: 10.1136/bmj.k3218. 50 citations

Funding included an *NIHR Health Technology Assessment* grant, 'Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children - a review of unpublished data' to the University of Oxford with C Heneghan as Chief Investigator, GBP390,553 (10/80/01, 2011-2016); and a grant to B Goldacre from the *Laura and John Arnold Foundation*, 'Public engagement in evidence based medicine and data', USD1,263,806 (2014-2019).

4. Details of the impact

The reviews of neuraminidase inhibitors [2,3]; the development of new methods [1] and the TrialsTracker [4]; and the resulting insights into compliance [5,6] have underpinned campaigns for

greater transparency in clinical trial reporting, influenced global changes in healthcare policy, and helped to hold public bodies to account.

Informing UK healthcare policy

Data from the UK National Audit Office confirmed that between 2006/7 and 2012/13, the Department of Health and Social Care spent GBP424,000,000 on oseltamivir ("Tamiflu") for use in a pandemic, but had to write off GBP74,000,000 of the stockpile [A]. Expenditure in the USA was reportedly in excess of USD1,300,000,000.

Following the first publication of the Cochrane review [2] in January 2012, the UK Parliamentary Public Accounts Committee called in 2013 for an inquiry into the UK government's policy of stockpiling antiviral drugs. Part of the remit was to explore "*the Cochrane Collaboration's updated review of Tamiflu and the ramifications that access to clinical trial data has for the whole of medicine."* The University of Oxford lead for the review, Heneghan, gave written evidence based on this research including reflections on the difficulties encountered in obtaining full information on trials for [2]. The Committee concluded that the failure of trial sponsors to share the full results of clinical trials undermined the ability of doctors, researchers and clinicians to make informed decisions about treatments, and thus undermined the use of medicines by the NHS [A].

In 2016, the University of Oxford researchers published an audit of the registration and publication of a set of clinical trials funded by the NIHR and undertaken at two large research units in Oxford, at the request of the associated Patient Involvement Working Group [B]. In March 2017, Goldacre gave written and oral evidence to the Parliamentary Science and Technology Commons Select Committee, drawing on this proof-of-concept audit and other work from the Oxford group. In 2018, the Select Committee's report "*Research integrity: clinical trials transparency*" recommended that the NHS "*should be provided with funding to establish a national audit programme of clinical trials transparency, including the publication of a single official list of which UK trials have published results and those which are due to but have not."* [C].

Based on these recommendations, the NHS Health Research Authority (HRA) launched the "*Make it Public*" campaign in June 2019, citing the 2017/18 '*Research integrity*' report [C]. The University of Oxford provided data from EU TrialsTracker to inform the consultation, which was acknowledged in a summary in the consultation document highlighting that '*around 25% of UK sponsors do not report results on time*'. The consultation stated that the HRA planned to change their processes to address this challenge and included proposals on how to improve reporting. [D(i)]. The resulting policy, 'Make it Public: transparency and openness in health and social care research', was published in September 2020 and outlined a vision for research transparency and an expectation that results be reported within 12 months of the study end date and annual publication of compliance rates [D(ii)].

Changing global healthcare policy

In 2015, on the basis of the work undertaken to establish trial reporting transparency for neuraminidase inhibitors [2, 3], the WHO commissioned the Centre for Evidence-Based Medicine (CEBM) at the University of Oxford to provide the background briefing document [E(i)] for the WHO consultation on data and results sharing during public health emergencies. The resulting WHO statement and consensus in September 2015 [E(ii)] resulted in the implementation of a new protocol for data sharing during the Zika outbreak of 2016 [E(iii)], that was subsequently important in the response to COVID-19. The Head of Research and Development at WHO said "*That work and the consultation it supported was very influential as the norms for sharing information prior to manuscript publication have shifted dramatically…. During the 2020 pandemic Medrxiv, Biorxiv and other preprint servers have become critical information sharing modalities; something that was called for during the 2015 meeting*" [E(iv)].

In May 2017 the WHO led the development of a joint statement on the public disclosure of results from clinical trials, in which various non-commercial funders, including the MRC, the Wellcome Trust and CEPI, committed to implement key trials transparency policies [F]. The Head of Research and Development at WHO confirmed that the Oxford researchers *"played key roles in helping to develop international standards around transparency in clinical research"* and that "*The joint statement has led to real changes in the policies of major funders*" [E(iii)].

In March 2017 an expert committee of the WHO, citing [2], recommended deleting the antiviral drug oseltamivir from the Core Essential Medicines List (the most efficacious, safe and cost-effective medicines for priority conditions) [G(i)] and transferring it to the Complementary List (medicines which are not necessarily affordable, or for which specialised health care facilities or services may be needed), where it has since remained [G(ii)]. The peer review report [G(iii)] making this recommendation noted that [2] "*includes data from the complete set of clinical study reports of clinical trials of oseltamivir*".

Increasing data transparency and compliance worldwide

In 2013, the University of Oxford (as the CEBM), Goldacre and the BMJ co-founded AllTrials.net, a global campaign for trials transparency. By 2020, AllTrials had 95,000 individual supporters, 727 organisations (including patient groups, academic bodies, drug companies), and advocates for all past and present clinical trials to be registered, with their methods and results reported in full. Following their 2018 report on 'Research Integrity' [C] and the launch of the EU TrialsTracker in 2018 [6], in early 2019 the Parliamentary Science and Technology Commons Select Committee asked Goldacre to provide data on the reporting performance of all UK universities and NHS Hospital Trusts. The Committee reminded all universities and NHS Hospital Trusts of their responsibilities (regardless of current performance) and demanded overall compliance to improve. For a follow-on hearing, Goldacre and AllTrials provided written evidence with updates on performance across all UK universities and Trusts to the Committee [H]. This evidence showed that in the 12 months following the publication of the report (Oct 2018 to Oct 2019), reporting rates for both UK university-sponsored and NHS Trust-sponsored clinical trials increased significantly (59.7% to 72.1% and 35.4% to 56.3% respectively, by October 2019 covering 1,349 trials due to report). It also resulted in warnings from the government to institutions with poor reporting levels.

In 2015, the European Medicines Agency (EMA) published its policy on clinical data for medicinal products for human use (EMA Policy 0070), which required that previously unpublished clinical reports (including clinical study reports) from central regulatory applications be published in an anonymised format [I]. Following publication of the EU TrialsTracker [6] in September 2018, the reporting rate of EU clinical trials rose rapidly over the subsequent 12 months [6] in September 2018, from 51.2% to 61.5%, and increased further to 68.1% as of December 2020 [J(i)]. Clinical trial reporting by industry has also significantly improved as a direct result of TrialsTracker. The Director of the Clinical Disclosure Office at Novartis stated that "*The TrialsTracker…helped allow Novartis to improve its excellent transparency compliance and achieve 100% compliance in the EU in 2020. In the US, we are proud to use these trackers to highlight our excellent compliance record.*" [K(i)]. Eli Lilly stated that TrialsTracker is used to provide monthly compliance reports and enabled them to meet EMA expectations [K(ii)].

The transparency advocacy organisation TranspariMED, citing TrialsTracker, reported that UK universities outperform European universities in clinical trial reporting [J(ii)], concluding that this was a result of combined pressure from parliament [C], research funders [F] and the media.

Holding public bodies to account to restore public trust

The findings from the Cochrane A159 review [2] were covered widely, criticising the money wasted on stockpiling unevidenced drugs. In June 2015, the UK Chief Medical Officer, concerned that widespread coverage could affect public trust negatively, asked the Academy of Medical Sciences to investigate how to restore public trust in scientific evidence for decision making. In their report (June 2017), 'Enhancing the use of scientific evidence to judge the potential benefits and harms of medicines', the Academy, cited the Cochrane review [2] as a case study in the introduction, stating that this emphasised "*the need for openness in decision-making processes to allow wider society to judge whether decisions are made based on sufficiently robust and relevant evidence*" [L]. Recommendation 5 of the report addressed the publication of research findings.

Following the publication of the Select Committee report on Research integrity [C], the Telegraph used the EU TrialsTracker to identify three unreported vaccine trials from Public Health England [M(i)]. As a result of this coverage, and pressure from Sir Norman Lamb MP, PHE apologised, citing the EU TrialsTracker [6], and reported the results of all three trials [M(ii),(iii)]. In December 2020, PHE was at 100% compliance on the EU TrialsTracker.

TranspariMED has consistently used TrialsTracker data to pressure academic institutions in the US and Europe, resulting in increased compliance. The founder of TranspariMED states that

"*TranspariMED has…used data from the Trials Trackers as the backbone of most of its advocacy work"* and that they *"have never encountered a data tool that has had such a dramatic and sustained positive impact on institutions' and regulatory bodies' behaviour"* [N(i)]. TranspariMED reports of clinical trial reporting by German universities, using TrialsTracker data, resulted in increased compliance [N(ii)]. TranspariMED also affirm that after they used TrialsTracker data for a report on compliance in the US, "*the majority of the universities flagged as having compliance gaps have substantially improved their performance*" [N(i)], illustrating the value of the FDAAA capabilities [5] developed by the DataLab team. Similar outcomes are described by TranspariMED in Austria, Denmark, the Netherlands and Spain [N(i)].

5. Sources to corroborate the impact

A. House of Commons Committee of Public Accounts Report HC295: Access to clinical trial data and the stockpiling of Tamiflu. 18 December 2013. Includes written evidence from the Cochrane Neuraminidase Review Group, headed by Heneghan, on 20 June 2013 (p.35).

B Journal article: Tompson AC, Petit-Zeman S, Goldacre B and Heneghan CJ. Getting our house in order: an audit of the registration and publication of clinical trials supported by the National Institute for Health Research Oxford Biomedical Research Centre and the Musculoskeletal Biomedical Research Unit. *BMJ Open* 6: e009285 DOI: http://dx.doi.org/10.1136/bmjopen-2015-009285

C. House of Commons Science and Technology Committee Report HC1480: Research integrity: clinical trials transparency. 23 October 2018

D. Health Research Authority (HRA) 'Make it Public' policy development (i) Strategy for consultation, June 2019. (ii) HRA Report, 'Make it Public: transparency and openness in health and social care research', September 2020.

E. World Health Organization policy development: (i) Goldacre B et al, WHO consultation on Data and Results Sharing During Public Health Emergencies: Background Briefing Paper, September 2015; (ii) WHO, 'Developing global norms for sharing data and results during public health emergencies' statement and consensus, September 2015, (iii) Data sharing in public health emergencies: a call to researchers, a protocol from the Bulletin of the World Health Organization, March 2016, DOI: 10.2471/BLT.16.170860 (iv) Testimonial from Head of Research and Development, WHO describing importance of Oxford research on WHO data sharing policies

F. WHO-led Joint Statement on public disclosure of results from clinical trials. May 2017

G. WHO (i) Model List of Essential Medicines, 21st list, 2019; (ii) 21st Expert Committee on Selection and Use of Essential Medicines; (iii) Peer Review Report [oseltamivir - deletion].

H. DataLab and AllTrials report for Sci Tech Committee, October 2019

I. European Medicines Agency policy on publication of clinical data for medicinal products for human use, Policy 0070, October 2014.

J. Improvements in EU trial reporting: (i) EU clinical trials data reporting status, December 2020 from https://github.com/ebmdatalab/euctr-tracker-data/blob/master/headline-history.json; (ii) TranspariMED report, 'Clinical trial reporting by European universities', April 2019

K Testimonials describing use of EU and US TrialsTrackers in assessing and improving clinical trial reporting compliance from (i) Director of the Clinical Disclosure Office, Novartis; (ii) Manager, Clinical Trial Registry Office, Eli Lilly and Company.

L. Academy of Medical Sciences Report: 'Enhancing the use of scientific evidence to judge the potential benefits and harms of medicines.' Jun 2017

M. (i) Telegraph article, 'Public Health England withholding vaccines results making it impossible to establish if drugs could be harmful', 15 Sep 2018 ; (ii) Response from PHE to Rt Hon Norman Lamb MP, Oct 2018; (iii) PHE Twitter thread referencing [6]

N. (i) Testimonial from Founder of TranspariMED, and (ii) TranspariMED report of German universities' clinical trial reporting.