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Access to Clinical Study Reports: mechanisms, barriers and benefits

An annotated bibliography

This annotated bibliography was originally compiled for TranspariMED's internal use. It is not intended to be comprehensive. Sources are listed in no particular order.

For a simple narrative introduction to Clinical Study Reports and why they matter, see the report *Clinical Trial Transparency: A Guide for Policy Makers*. For case studies, see *A Key to Better and Safer Medicines*. Both contain additional references to the relevant literature.

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EMA Clinical Data Publication (CDP)
Presentation by Karen Quigley, EMA Documents Access and Publication Service, April 2018

- Overview of Policy 0070 contents and implementation
- Type of published documents
- Over 4,000 users have viewed 160,000 documents to date
- EMA only redacted 134 pages out of 1,308,244 pages (0.01%) due to CCI
- Details on redaction process

Clinical study reports should be available to help clinicians and patients make informed decisions
Nav Persaud and Art Slutsky, BMJ, June 2018

- Argues that CSRs "should be made available to help clinicians and patients better make informed decisions"
- "The doxylamine-pyridoxine trial was reported three times and it was approved twice by the FDA, but the details in the clinical study report indicate that the medication effect is not clinically significant."
- "Concerns about releasing individual participant level data do not apply to the methodological details in the clinical study report."

RIAT Clinical Study Report: glossary webpage
RIAT Support Center, 2018

- Users can browse or download a sample CSR
- "CSRs represent the most complete synthesis of the planning, execution, and results of a clinical trial."
- "CSRs generally contain, as appendices, important study documents including the study protocol and amendments, statistical analysis plan and amendments, case report forms (CRFs),… certificates of analysis,…"

RIAT Regulatory Resources: webpage
RIAT Support Center, 2018

- Provides guidance on how to access documents: EMA, FDA, Australia, Canada
- FDA access:
    - "We are only aware of one occasion where some parts of a CSR were released [by FDA] in response to a FOIA request, and a second occasion when CSRs were released under FOIA but only after the requestors sued."
- EMA access:
    - Policy 0043: Can request access to older Clinical Study Reports
    - Policy 0070: Prospectively for compounds on which it has made a decision under the centralised procedure since 1 January 2015, incl. one or more CSR main bodies
    - European Public Assessment Reports (EPARs) are readily accessible with no restrictions and contain details of EMA's scientific assessment

ClinicalStudyDataRequest.com website

- A single entry portal for accessing clinical study reports and electronic individual participant data [accessed August 2018]
- 19 companies and non-profit sponsors currently participate
- Requires requestors to develop a full research proposal plan and submit it for review
- All sponsors have limitations on data release that are generally enforced by requiring requestors to sign a Data Use Agreement (DUA) prior to data access

Legal Impact Assessment of Brexit: Clinical Trials Data
SFL Regulatory Affairs and Scientific Data GmbH, June 2018

- Disclosure of clinical data to regulatory authorities is covered by WTO's legal IP framework
- May only disclose if (1) superseding public interest and (2) measures against unfair commercial use [TRIPS agreement Art 39(3)]
- Discusses frameworks: UNESCO, WHO, IN ICESCR
- Discusses European Union laws, regulations, policies, court cases
- EU Clinical Trials Regulation expected to apply from YE 2019: Art 37 mandates CSR disclosure within 30 days of end of marketing authorization process

Clinical Data Summary Pilot Program (see also the FAQ)
FDA webpage, 2018

- Pilot program of up to nine recently submitted new drug applications (NDAs) whose sponsors volunteer to participate
- FDA will release portions of CSR body, the protocol and amendments, and the statistical analysis plan
- Redactions:
    - FDA itself will redact selected portions of the CSRs for trade secrets, confidential commercial information, and personal privacy information
    - Redactions made in line with current FOI practice
    - The sponsor will not have an opportunity to review redactions before the CSR is posted
- Links to Drug Approval Package for ERLEADA (apalutamide) which includes CSR for pivotal clinical trials, not for all studies in the application
- After pilot program is complete, FDA will seek public feedback through a Federal Register notice and docket for public comments

Access to Information and the Right to Health: The Case for Clinical Trials Transparency
Trudo Lemmons and Candice Telfer, American Journal of Law and Medicine, 2012

- Discusses implications of TRIPS Article 39:
  - States must protect confidentiality of data "except where necessary to protect the public" or "where steps are taken to ensure that data is protected against unfair commercial use"
  - Where companies have shared data voluntarily, the state is no longer bound by confidentiality obligation
  - Data exclusivity "de facto extends patent protection" and raises entry barriers for generics companies

GHJP Closes Two-Year FOIA Case Against Drug Manufacturer
Treatment Action Group and Yale University, 2017

- FOI with FDA covered two costly Hepatitis C drugs, Sovaldi and Harvoni
- Gilead stonewalled and refused to share data
- Obtained CSRs as well as study protocols, case report forms on adverse events, and selected correspondence between Gilead and the FDA
- FDA withheld IPD, and Gilead refused to share it

Questions and answers on the European Medicines Agency policy on publication of clinical data for medicinal products for human use
EMA, June 2015

- "in parallel to other processes for providing clinical reports to HTA bodies, if HTA bodies would like to have access to clinical reports within the frame of this policy, nothing in the ToU will prevent HTA bodies from having access to and use of the clinical reports for the purpose of their institutional activities. The HTA bodies can download, transcribe, cut and paste and print the data in accordance with the specific ToU for academic and other non-commercial research purposes."
- "It is for the Agency to take the final decision on what is and is not to be redacted. The extent of what the Agency will redact will always be visible in the final documents that the Agency makes available."

Submission of comments on 'Policy 0070 on publication and access to clinical-trial data'
IQWiG, no date

- "There is overwhelming evidence, that so far publicly available trial data are insufficient to provide a complete and unbiased picture of a given health care intervention. HTA needs additional independent and high quality data sources. Data submitted to regulatory agencies are therefore required by IQWiG and other HTA agencies. However, the data held by EMA are not only important for HTA agencies but also for other researchers supporting evidence-based decision making in health care and should thus in general be made publicly available."
- "IQWiG's own work has shown that clinical trial documentation held by regulatory agencies provides substantial additional information compared to publicly available trial reports."

EMA Policy 0070: Data Utility in Anonymised Clinical Study Reports (CSRs)
Jean-Marc Ferran and Sarah Nevitt, PhUSE Data Transparency Working Group, 2017

- Provide data on requests made under Policy 0043 in 2016 (32% of pages by academics)
- An "Interim guidance on the inclusion of Clinical Study Reports and other regulatory documents in Cochrane Reviews" is being developed
- The value of the information within CSRs is becoming increasingly recognised within the
- academic research community
- Discusses efficiency gains in pharma research through access to CSRs: "In the case of drug repurposing (from e.g. a frequent to a rare disease area), having access to all previous data is of the utmost importance and would speed up the process."
- Access to CSR appendices can be vital to studying drug harms (p. 19+21)
- Jeppe Schroll: "current EMA policy redacts important information about when the adverse events appeared as well as what they were. Newer CSRs does not have individual adverse event listings and the EMA are not even in possession of them." (p.22)
- Contains appendix listing academic studies based on CSRs and bibliography

Submission of comments on 'Policy 0070 on publication and access to clinical-trial data'
IQWIG submission to EMA, 2013 [EMA/240810/2013]

- "Since HTA is comparing new interventions to currently available therapies, full information on study methods and study results is required for all drugs in current use. IQWiG therefore suggests that EMA makes available all clinical study reports available at the agency from past or future submissions for any drug approved in Europe. Restricting the policy to data submitted after the policy comes into effect is insufficient to meet HTA and public health requirements."
- "While IQWiG appreciates the fact that EMA can only make available data submitted to the agency, the final goal of EMA's transparency initiative should be availability of all studies on a given drug (or even more on all drugs, devices or other health care interventions). Therefore, IQWiG would like to suggest that EMA expands the trial database to allow for posting of clinical study reports of all studies on a given drug (or even more on all drugs, devices or other health care interventions). The pharmaceutical industry and other trial sponsors could then also release clinical study reports of studies not submitted to EMA in this central database, thus underlining their commitment to transparency."
- "IQWiG supports the classification of categories of access as provided in Annexes I and II of the policy."

Finalisation of the EMA policy on publication of and access to clinical trial data – Targeted consultation with key stakeholders in May 2014
EMA, 2014

- "Academia, research bodies and medical journals, as well as consumers organisations and HCPs organisations criticised the view on screen only concept. They considered that it was too limited as only view on screen. Academia and research bodies questioned the usefulness of view of screen and disagreed with this type of access envisaged making it unworkable. View on screen was seen as an impediment to serious researchers rather than a way to prevent unfair commercial use. They sought assurance that at least the data would be searchable."

Final advice to the European Medicines Agency from the clinical trial advisory group on Clinical trial data formats
EMA, 2013

- Lists data types routinely requested by EMA
- Not included: ICH E3 16.3 Case Report Forms and IPD
- "Of note, old CSRs may not fully comply with the current ICH E3 format. In this case, it will be acceptable to provide the CSR in the original format in which it was written."
- "The general view is that re-formatting of old data should not be requested by EMA; however, some are of the opinion that EMA should ask the marketing authorisation holder to provide the data in a format which is machine-readable and can be done with a non-proprietary software."

Reviving the FDA's Authority to Publicly Explain Why New Drug Applications Are Approved or Rejected
Matthew Herder, Health Care Policy and Law, July 2018

- FDA pilot program so far is voluntary "notwithstanding the FDA's sound legal basis for disclosing the safety and effectiveness data contained in clinical study reports as summaries of clinical studies"
- In Canada, regulations that aim to copy the European approach are pending in Parliament.

Secrecy or transparency? The future of regulatory trial data
Beate Wieseler and Natalie McGauran, CMAJ, Feb 2017

- Discusses a study of duloxetine in which CSRs contained information on psychiatric adverse events found in "none of the journal publications or registry reports of the four trials under study"
- Notes that authors of that study reached different conclusions from the EMA even though both had been looking at the same data
- Flags US Institute of Medicine's proposals for sharing CSRs and IPD
- Suggests that "analyzing clinical data published on the EMA's website should become a standard approach for systematic reviewers"
- Accuses industry of "obstructing transparency gains, for example, through the new European Union trade secrets directive"

EMA scales back transparency initiatives because of workload
Peter Doshi, BMJ, August 2018

- EMA has suspended the proactive release of new Clinical Study Reports (policy 0070) until March 2019, citing the extra workload incurred by its relocation from London to Amsterdam.
- In addition, from now onwards, only European Union citizens will be able to request access to old CSRs (policy 0043) – this policy shift is not temporary
- Summarized in this TranspariMED blog post

Beyond journal publications - a new format for the publication of clinical trials
Beate Wieseler, Z Evid Fortbild Qual Gesundhwes., Feb 2017

- Argues that journal publications are strongly biased and flawed, and efforts to fix them unsuccessful, that they "should no longer be considered the primary source of information" on clinical trials
- Need for access to full protocols, CSRs (including Case Report Forms), and IPD

New EMA Policy—Further Measures Needed to Support Comparative Effectiveness Assessments
Beate Wieseler, JAMA, Nov 2014

- CSRs made available under EMA policy 0070 only prospective, which means that "information on established drugs (ie, approved before the effective date of the policy) will still remain biased, even though they will account for the lion's share of drugs prescribed in clinical practice for years to come. This imbalance will hamper a meaningful comparison of established and newer drugs and therefore devaluate comparative effectiveness research… In addition, open questions on established drugs will never be answered."
- "With the technical possibilities regulatory agencies offer, it would be easy to fill the existing evidence gap and post clinical study reports of all established drugs (or drugs that were never approved) in a central repository."

Challenges of independent assessment of potential harms of HPV vaccines
Lars Jørgensen et al, BMJ, Sept 2018

- "After three years, we had obtained just 18 Clinical Study Reports (62% of the EMA's 29 reports)… Unfortunately, the reports still lacked important sections, such as protocols and serious harms narratives… Only three reports included completed case report forms… One study report of 4263 pages was released in 17 files across seven batches over 12 months."
- "[EMA correspondence confirmed that] for some studies, the Clinical Study Reports that industry provides to EMA are incomplete (eg, missing appendices)."
- "[R]egulators should release complete and coherent Clinical Study Reports… Urgent changes are essential for open and transparent assessment of the harms and benefits of interventions."

Benefits and harms in clinical trials of duloxetine for treatment of major depressive disorder: comparison of clinical study reports, trial registries, and publications
Emma Maund et al, BMJ, 2014

- "Clinical study reports contained extensive data on major harms that were unavailable in journal articles and in trial registry reports."
- "There were [usually minor] inconsistencies between protocols and clinical study reports and within clinical study reports."
- Since 1995, CSRs submitted to regulators must follow the International Conference of Harmonisation (ICH) E3 guideline
- The EMA did not hold protocol appendices for two trials that contained information on the analysis population
- Two of nine trials reviewed had not published their results; one had published its results misleadingly
- "Clinical study reports should… be the primary data source for systematic reviews of drugs. This requires public access to these documents."

Using Clinical Study Reports versus published articles in a Cochrane Review update

V. Musini et al, poster presentation, 2016

- Five advantages of including CSRs in systematic reviews:
    1. comprehensive information on study methods
    2. availability of numerical data with standard deviation instead of graphs
    3. availability of data of all secondary outcomes as stated in the protocol
    4. opportunity for accurate assessment of risk of bias of each included study
    5. provision of detailed information for all-cause mortality, non-fatal serious adverse events and specific adverse events

Information on new drugs at market entry: retrospective analysis of health technology assessment reports versus regulatory reports, journal publications, and registry reports

Michael Köhler et al, BMJ, 2015

- "Conventional, publicly available sources provide insufficient information on new drugs, especially on patient relevant outcomes in approved subpopulations."

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