Gaps in preclinical and clinical data: A need for transparency in the regulatory evidence base

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• An independent patient safety charity
• Our aim is to make medicines safer, through far greater use of more predictive human-relevant science
• See: www.SaferMedicines.org
Problem?

- Negative data missing / non publication
- Quality of data questionable
- Lack of standards
- Bias data reporting from sponsors, bias data removal

**Improved data transparency needed to**
- Reduce repeated experiments
- Reduce cost and resource use
- Knowledge gain
- Improved efficiency of trials and clinical outcomes

All data needs be more widely available – regulators sitting on data??
Impact of poor preclinical reporting – quality/standards

- Pre-clinical animal studies assessed against the benefits for humans
- All the studies were of poor quality
- Less than 7% of the studies were permissible according to Bateson’s Cube

Findings indicate a pressing need to:
- review regulations, particularly those that permit animals to suffer severe harms
- reform the processes of prospectively assessing pre-clinical animal studies to make them fit for purpose; and
- systematically evaluate the benefits of pre-clinical animal research to permit a more realistic assessment of its likely future benefits

The regulatory systems … failed to safeguard animals from severe suffering or to ensure that only beneficial, scientifically rigorous research was conducted


EBTC Scientific Symposium #4: Overcoming data availability obstacles in the way of evidence-based toxicology
Friday 25 June 2021
Impact of poor preclinical reporting – selective reporting

TB vaccination booster MVA85A

- Investigation by *The BMJ* (2018)
  - Results of animal studies selectively reported to gain funding and approval for human trials
  - Privately playing down or dismissing unsupportive experiments as “failed” or irrelevant
  - Major funders of TB research to rethink their funding priorities, with allegations that this has slowed progress in the entire field.
Impact of poor preclinical reporting – selective reporting

Investigator brochure

None of the animal studies were mentioned in the October 2006 investigator brochure, despite several being already published.

Not all raw data from Sharpe et al is included — Kaplan-Meier survival plot cannot be derived.

These three studies do not show benefit from an MVA85A boost and are not fully referenced in any investigator brochures.

The investigation asks whether the parents of babies included in the South African trial were misled...
Impact of poor preclinical reporting – publication bias, poor data quality and lack of standards in EB decision making

**Evidence Stream 1**

Limitations of the Published Literature

- **Publication bias:**
  - Regulatory preclinical and clinical studies tend not to be published
  - Need incentives for industry and regulatory agencies to make data used in approval processes for NDA and MAA public!

- **Publication quality:**
  - Lack of detailed protocols
  - Lack of individual animal data
  - Insufficient details in the methods section
  - Selective reporting

- **Publication standards:**
  - Lack of structured abstracts
Impact of poor preclinical reporting – non-publication


- n = 210 archived animal study protocols of two major German UMCs (university medical centres)
- tracked results publication
- Overall non-publication of 33% of all animal studies

Study confirms that the non-publication of results from animal studies conducted at UMCs is relatively common

Results dissemination should become a professional standard for animal research. Academic institutions and research funders should develop effective policies in this regard

"Preregistration of preclinical studies could provide a helpful tool"
Preclinical reporting solutions

Prospective registration on an online, accessible platform to increase transparency and data sharing

www.preclinicaltrials.eu

Pre-registration of preclinical studies

“One of the problems that we have at the FDA in this regard is that trade secrets at the FDA are protected by the law. And I’ve always felt that one of the most important things that could be done, if it could be, would be free up all the data from the drug development process that is never seen by anyone,” he said at the event hosted by the National Library of Medicine.

“Because there is no compelling reason to publish them. If they’re successful, they become trade secrets. And if they’re unsuccessful, they get dropped and no one cares if they’re published,” he continued. “If you think reproducibility and the fabric of science, in some ways, if it were possible, it would really good to have something like a ClinicalTrials.gov for preclinical work.”

FDA Commissioner Robert Califf, 2016
Clinical trials reporting

- 2017 - transparency expectations tightened for clinical trial sponsors (Final Rule)
- Investigations in 2019/20 found many drug makers and academic institutions continually failed to comply, widespread noncompliance and study results were reported long after statutory deadlines or not at all
- 216 trials, 2/3rds unreported results by due date, and averaged 268 days late
- Only 17% of the 216 trials had submitted results
- Of 184 sponsor organizations with at least five trials, 30 companies, universities, or medical centers never met a single deadline

The goal is to ensure that each trial contributes accurate and complete information to the medical evidence base—eliminating “secret trials” or biased reports with misleading conclusions.
ICMRA & WHO statement

**Call for**
- The Pharmaceutical industry to provide wide access to clinical data for all new medicines and vaccines
- Clinical trial reports should be published without redaction of confidential information for reasons of overriding public health interest

**The priority**
- To improve transparency and strengthen the validity and value of the scientific evidence base
- Both positive and negative clinically relevant data should be made available (personal data and individual patient data should be redacted and anonymisation can be used)

Owed to trial participants who contributed physically and took potential research risks

“Regulators continue to spend considerable resources negotiating transparency with sponsors”

“Often, initiatives are reliant on goodwill or lack appropriate resourcing”
SEND - A Standard for Exchange of Nonclinical Data

- Supports data typically found in single-dose general toxicology, repeat-dose general toxicology, and carcinogenicity studies, as well as respiratory, cardiovascular and more recently DART testing conducted during safety pharmacology studies.

- All studies started after December 15, 2016 supporting IND and BLA submissions to FDA need to be compliant with SEND.

- The Japan Pharmaceutical Manufacturers Association (JPMA) SEND Taskforce Team has investigated the quality of the data in SEND domains and has indicated that variations found should be reduced, leading to higher quality datasets with powerful and increased searchability before adoption in Japan.

- The EMA has expressed interest and is recommending the use of SEND.
EPA - Toxic Substance Control Act (TSCA)

- Commitment to making evidence-based decisions and developing policies and programs that are guided by the best available scientific data.
- TSCA reform – section 4 (h) to decrease testing in vertebrates – industry consortia to jointly conduct studies to prevent duplication.

Maureen Gwinn, EPA Center for Computational Toxicology and Exposure,
Updates on Activities Related to 21st Century Toxicology
(CAAT webinar, 12th May 2021)
ICE (Integrated Chemical Environment) database

- Curated data and tools from NICEATM, its partners, and other resources to facilitate the safety assessment of chemicals
  - PBPPK tools
  - IVIVE tools
  - Chemical characterization tools
  - Annotated chemicals – MOA, mechanistic assays and physicochemical property data

- High-quality data, freely available and formatted for use in computational workflows

- Includes data from animal and non-animal tests that measure toxic effects described in chemical safety regulations e.g. oral toxicity, skin and eye irritation, skin sensitization, and endocrine activity
Tox21 / EuToxRisk

Tox21 platform (EPA/NCATS/NTP/FDA)

- High quality bioactivity data assembled into dataset/platform
- Allows the development of models with better translatability for human biology
- Includes over 70 screening campaigns with approximately 10,000 chemicals including both approved and rejected drugs, pesticides and industrial chemicals
- >100 papers and 100 million data point database for toxicology.

Knowledge platform

- 150 test method descriptions
- >1000 datasets (BioStudies database)
- 14 Case studies (e.g. 5 Read across studies published and reported to OECD IATA WG)
- >140 publications
FDA – NAMs development

• FDA’s Roadmap describes leveraging research to identify data gaps and oversight by the Commissioner to transparency and knowledge sharing

• Need to expand acceptable assays in regulatory submissions to include human relevant in vitro and in silico methods – AMWG

• “Regulators will incorporate NAMS if regulatory standards are met”

• BUT regulatory studies are not in the public domain
Transparency in the regulatory evidence base is needed

- Need to publicise all data, negative or positive
- Improve quality of data
- Implement standards in reporting
- Prevent bias data reporting
Transparency in the regulatory evidence base

Benefits:
• Avoids repetition of unnecessary trials / waste of resources (human, animal and financial)
• Improves efficiency of development programmes
• Reduces both development costs and time
• Allows secondary analyses (and meta-analysis) which have a different or complementary focus
• Democratizes access to data
• Increased public scrutiny should eventually improve the overall quality of data

Public trust and scrutiny of regulatory decisions is needed

Owed to trial participants who contributed physically and took potential research risks
Reporting outcomes

- Reporting guidelines and protocols have been developed for clinical trial reports
  - Consolidated Standards of Reporting Trials (CONSORT)
  - Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)
- But more detail is needed to adequately describe trial outcomes
- Key information - how trial outcomes were selected, defined, measured and analysed - is often missing or poorly reported
- Notably, 40%-60% of trials have been found to have at least one primary outcome that was changed, introduced or omitted between protocol and publication

Without clear and complete reporting of trial outcomes, researchers cannot adequately appraise, consolidate or replicate findings, hindering the translation of evidence into clinical practice and policy
Clinical Trial Transparency – COVID19 vaccines

- Vaccine manufacturers disclosed full clinical study protocols for their late-stage randomized, blinded, placebo-controlled studies.
- Experts continued to seek more details on statistical analysis plans for assessment of ADRs and research outcomes.

COVID-19 Vaccine Concerns Prompt Clinical Trial Transparency

September 21, 2020
Jill Wechsler, Pharm Exec’s Washington Correspondent

With all eyes on efforts to research and test potential vaccines and therapies to combat the coronavirus pandemic, fears about overly accelerated development programs have heightened demands for wider access to information on study protocols, statistical analysis plans, and early results.
NCATS COVID-19 OpenData Portal

- Created to openly share COVID-19-related drug repurposing data and experiments for all approved drugs
- Developed using SARS-CoV-2-related assays to screen over 10,000 compounds
- The scientific community can use the data for a variety of drug repurposing activities