BMTS 2019

CBMRT

Building a Network of Research Transparency Ambassadors

Hello,
Welcome to CBMRT's second newsletter - we're excited to share with you the key points to emerge from our first European Biomedical Transparency Summit, held on May 15th in Paris, France. **If you couldn't attend, read on to catch up on what you missed!**

In line with its mission to increase transparency in biomedical research practices, the Center for Biomedical Research Transparency (CBMRT) hosts a free 5-year Biomedical Transparency Summit (BMTS) series in the US and Europe. The goal of BMTS is to promote discussion and collaboration amongst diverse stakeholders in the movement towards greater transparency at a global level. Our first European BMTS was very well received, due in large part to the high quality of the speakers and panellists, and the enthusiasm of participants who travelled from across Europe as well as from the US. Wellcome Trust funding enabled a large number of early career researchers to attend; something CBMRT is keen to expand at future Summits, along with the representation of patient-centered research organizations. Here are some of the highlights:

The future of clinical trial reporting guidelines is… brightening

Professor Ravaud (Director, INSERM Epidemiology and Biostatistics Research Centre) provided a thoughtful account of the state of clinical trial reporting guideline adoption. Published in 1996 and endorsed by over 600 biomedical journals, CONSORT (Consolidated Standards of Reporting Trials) and its extensions comprise a 25-item reporting checklist for authors on trial design, analysis and interpretation. Whilst a 2012 Cochrane review found that checklist items were more completely reported in trials published in journals endorsing CONSORT than in non-endorsing journals, the overall reporting of key methodological items across all journals was “dismal”. And more complete reporting was found in results posted to clinicaltrials.gov than in published articles.

More recently however, an online writing aid tool called COBWEB has been developed for authors when writing the first draft of their article. It provides a template with each CONSORT item reported with the key elements that need to be presented in the form of several bullet points, along with an example of adequate reporting. A 2015 BMC Medicine study found that the use of COBWEB improved the completeness of reporting the results of randomized controlled trials.

> *I am but a simple trialist…*

Whilst there has been progress, scope clearly remains to address underlying reporting quality/completeness issues. COBWEB is yet to be formally launched, and there remains a lack of familiarity with and awareness of CONSORT (and its extensions) amongst researchers. Some items are difficult to understand, and there are numerous other relevant reporting guidelines beyond CONSORT (eg Tidier) – and yet more in the pipeline. Furthermore, there is no active implementation of CONSORT by most of the journals; authors are asked to comply but there is no enforcement. Options are being explored to address these challenges, including simplification of CONSORT and its extensions, improving awareness and compliance, and providing training to authors/reviewers.

Cochrane and Transparency

Founded in 1993 with a mission promote informed health decision making by producing high quality systematic reviews, Cochrane continues to be driven - in the face of changing evidence and pressure to provide more open access – by the reflection of Archie Cochrane 40 years ago:

> *"It is surely a great criticism of our profession that we have not organised a critical summary, by specialty or subspecialty, adapted periodically, of all relevant randomised controlled trials."*

Dr. David Tovey (outgoing Editor-in-Chief of Cochrane Library) described the move away from a reliance on data published in scientific journals towards fuller, more comprehensive, granular and 'real world' data. There is also widespread demand for results/data to be made available much more quickly, and for the inherent knowledge to be better translated for use by those who need it to make health decisions.

For its part, Cochrane is beginning to implement 'living systematic reviews' which aim to maintain reviews with data updates almost in 'real time'. It has increased content linking, multi-lingual content and added a PICO (Population, Intervention / Comparator, Outcome) search annotator to its library. Dr Tovey observed that machines have increasing capability to undertake some of the 'heavy lifting' of review production, and other tools such as RobotReviewer can help to assess risk of bias. He also noted the opportunity to better involve journalists in the process of accurately translating science to the public.

Plan S and Wellcome Open Access

An early stakeholder in the open access movement, Wellcome was the first major funder to implement an open access policy in 2000 and was the first Plan S funder to put technical details on how a funder could implement an open access policy to support Plan S. Dr Diego Baptista (Wellcome Open Research Coordinator) highlighted some of key elements of Wellcome's open access policy which has recently been revised to align with Plan S and will take effect on January 1, 2020:

- ✓ *All Wellcome-funded articles must be made freely available immediately upon publication under a CC-BY licence.*
- ✓ *Wellcome will no longer fund open access publication costs in subscription journals (unless journal has transformative open access agreement – support until 31.12.21)*
- ✓ *Publications regarding public health emergencies must be published immediately before peer review on an approved platform - this is a new requirement.*
- ✓ *Wellcome-funded organizations must sign or publicly commit to DORA (San Francisco Declaration on Research Assessment) – also new.*

Dr Baptista emphasized how Wellcome sees DORA as a key enabler of open access and is jointly funding a DORA community manager to support its implementation. Widespread adoption of DORA should ultimately see researchers being assessed based on the research they have conducted and its societal impact; the actual venue of publication becoming less of a driver. The Wellcome Open Research platform is similarly enabling; papers are published within 28 days of submission (with average APCs of £825 (free for Wellcome grantees)) and the open peer review process takes on average 72 days.

Clinical data sharing landscape

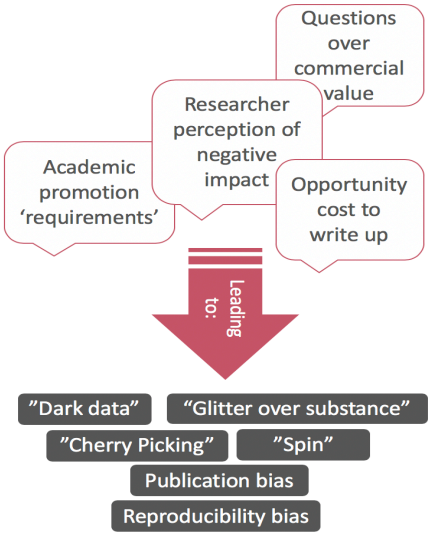
Scott Martin (Chair of ClinicalStudyDataRequest.com) described the opportunities for innovative data-driven research provided by the CSDR platform of over 3,700 studies shared free of charge by a consortium of 21 data providers. Since going live 5 years ago, access to patient-level data has been provided for 240 proposals, and 42 resultant studies have been published, with an additional 28 in the pipeline.

The consortium would however like to see a much stronger pipeline and is working to identify and address the underlying data sharing challenges on both the demand and supply side. Specifically, why are there not more proposals being submitted by researchers? Are researchers aware of the platform (and others like it) and its functionality. And do they have adequate support (including funding) to make use of it? On the supply side there are data management issues which revolve around the transformation of differently formatted datasets such that it is usable in the controlled (to ensure patient privacy) SAS environment provided by CSDR.

Mr Martin acknowledged that there are several other clinical data sharing platforms available which are likely experiencing similar challenges; but it is still early days – another 2 to 3 years is required to address these challenges and see the opportunities presented by CSDR fully realized.

The Null Hypothesis is now on your lab/kitchen table

Dr Sandra Petty (CEO, the Center for Biomedical Research Transparency) provided an update on CBMRT's Null Hypothesis (H_0) initiative. The goal of H_0 is to help address the systematic issues associated with publishing negative, inconclusive and replicative results:



Despite the importance of reporting research outcomes, many experimental results remain unpublished, sitting in lab books around the world ("dark data").

> *"As a physician, this issue is concerning; it is no less concerning for patients. To quote one of my astounded patients: "Don't you know all this already?!""*

H_0 is a home for well-designed yet negative or inconclusive studies, and replication work that is difficult to publish presently through traditional scholarly channels. Dr Petty emphasized the significant value in publishing these under-reported research outcomes in terms of informing future research design, reducing funding wastage, and promoting patient safety. H_0 is published in partnership with major scholarly societies and journal publishers using their existing infrastructure to source and peer review papers.

In partnership with Neurology® and the American Academy of Neurology, CBMRT launched Neurology® H_0 in 2018. The accepted papers appear online ahead of print on the Neurology® website, and are then printed together as a special issue. The first print edition of Neurology H_0 circulated as a special edition in April 2019 to over 34,000 subscribers. The H_0 concept will be expanded into other therapeutic areas over 2019, the goal being to build momentum and positive exposure for the write-up and publication of negative, inconclusive, and replicative research studies.

Beyond open access: Open peer review

Chief Editor of BMC Medicine (the flagship medical journal of the BMC group) Dr Lin Lee presented a delightfully data-rich case for open peer review. Her journal has had an open peer review system since its launch in 2003 and has been keenly tracking progress in a changing environment:

> *"Forty-four of the BMC series medical journals use only open peer review, with no opt out for authors or reviewers. These journals publish over 8,000 papers a year, demonstrating that at least in the medical disciplines, there is clearly a community willingness to undertake open peer review."*

However, there are ancillary issues, specifically: why are reviewers more reluctant to sign up for open peer review? Are quality, accountability, accept/reject drivers the same for open peer review? And what does it all mean for editors? Dr Lee cited results from a recent meta-analysis study which suggest that the quality of the peer review report is higher and the recommendation to reject manuscripts for publication is lower under an open peer review process.

> *"It's naïve to think that open peer review does not have any effect on editorial processes, so editors need to be mindful. Although generally we do not see differences in recommendations/report quality in open peer review, this does happen in specific instances and there must be editorial mechanisms to deal with this."*

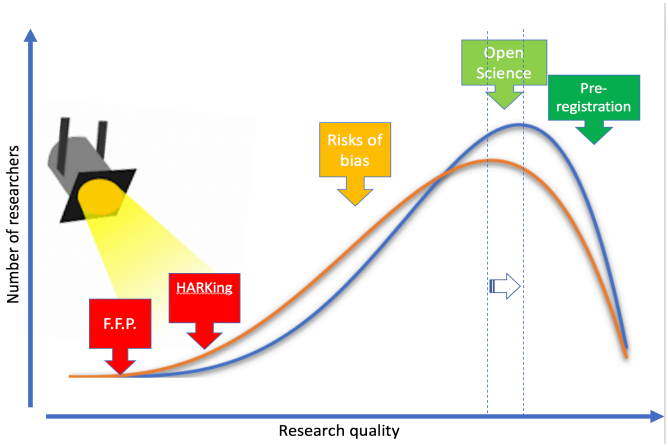
Trans-lation or cis-lation: How do we know if we know enough?

In setting out to answer this question Professor Malcolm Macleod (Professor of Neurology and Translational Neuroscience, University of Edinburgh) first described some of the challenges inherent in current animal research practices. Specifically, individual research (as opposed to meta-analyses) claims are unreliable because they are at high risk of bias. And even systematically collated meta-analyses can overstate effects given the partial or non-reporting of many experimental findings. Furthermore, the predictive value of animal research is not fully known (take for example a recent study of 1,026 in vitro and in vivo interventions in experimental stroke; of these just one was found effective in clinical trial). A lack of methodological rigor more generally negates replication efforts and works to bias results.

Bias and lack of rigor have significant implications in terms of wasted research funds (around $300 billion p.a. is spent on medical research globally (€50 billion in Europe)). - the widely cited Glasziou & Chalmers estimate is that up to 85% of this spend may be wasted.

> *"Even if waste is 'only' 50%, improvements which reduced that by 1% would free $3bn globally, €500m in Europe, every year. Investing around 1% of research expenditure in improvement activity would go a long way."*

Professor Macleod emphasized the need to get the basic building blocks of research design, conduct, analysis and reporting right and to correct biases inherent in current practices; otherwise research funding will continue to be wasted (and the amount of valid information gained from animals used in research will not be maximized). In considering the 'bell curve' of researchers and their practices, any research improvement strategy should first focus on 'shining the spotlight' on the poorest of practices to shift this bell curve rightwards; open science has a significant role to play in this process:



*FFP = fabrication, falsehood, plagiarism; HARKing = hypothesizing after the results are known.

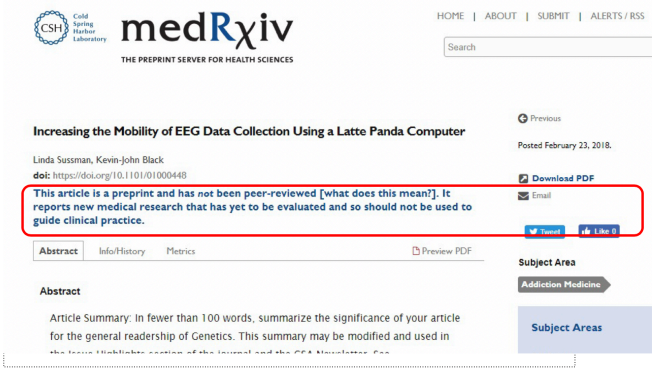
Professor Macleod suggested that there is a threshold summation of knowledge from animal experimentation that should be reached before this knowledge can be translated to human study (i.e. the point where “we know enough”) and that this point is probably at around 130 to 140 studies across animal types for a given intervention.

Pre-prints for clinical medicine

Dr Theodora Bloom (Executive Editor, BMJ) described the near exponential growth in preprints over the last 5 years; driven by an increasing preference for research funders to see ‘interim research outputs’, along with a greater openness to preprints as part of grant applications. Some funders are also providing guidance on how to choose a preprint repository and are launching their own open research platforms which provide a streamlined pipeline from pre-print through open peer review to submission for publication (Wellcome, Gates). There is also a generational aspect, with younger researchers more likely to preprint. It is noteworthy that an estimated two-thirds of preprints end up being published.

Dr Bloom also noted the balance to be struck between the benefits of more rapidly and openly sharing results and the potential risk to patient safety of sharing results that have not been fully peer reviewed. As BMJ’s representative in discussions towards launching the eagerly awaited medRxiv clinical preprint server, Dr Bloom is involved in the design of medRxiv’s measures for balancing speed against risk mitigation. These include up front screening and author undertakings, a series of automated, CSHL and affiliate checks, and escalation of ‘high risk’ preprints to medRxiv management.

Coming soon…



AllTrials update: More people are monitoring clinical trials results than you might think

Dr Sile Lane (Head of International Campaigns & Policy, Sense About Science) rounded out the Summit with an upbeat update on the AllTrials campaign which was launched in 2013 and calls for all clinical trials to be registered and results reported. The AllTrials US Trialtracker (which tracks FDAA registered clinical trials) shows that 63% of registered trials have been reported; the EU TrialTracker (which tracks clinical trials on the EU register) indicates 56% of trials have been reported.

Sponsor-level TrialTracker data are being monitored by a growing number of stakeholders to ultimately drive greater transparency in clinical trial reporting. At present 68% of registered company-sponsored trials have reported results, compared with just 11% of registered academic trials reported, prompting various stakeholders to act:

- ***UK House of Commons 2018 Report**: Research Integrity: Clinical Trials Transparency resulted in letters being sent to vice chancellors/rectors giving them 6 months to report their results – on parliamentary record.*
- ***Universities Allied for Essential Medicines**: Students taking action on campus to urge universities to improve their clinical trial reporting and to sign the WHO Statement on clinical trials transparency.*
- ***NHS Health Research Authority**: will no longer fund further clinical trials for grantee who has not reported.*
- ***Investment groups** monitor/support clinical trial transparency as an additional means of tracking pharma performance; pharmas in turn motivated to protect revenue/reputation.*

As quipped by Dr Lane, “writing letters makes a difference”: the AllTrials has made a significant positive impact by generating publicity, publishing reports, challenging regulators, meeting with companies and agitating for new practices in large research funders, trial centers and professional and ethics bodies. The challenge remains to expand this impact to a higher level of clinical trial results reporting – an increasingly urgent task as people and software retire.

Thanks again to our fantastic speakers, panellists and participants for making BMTS'19 Europe a success. We've uploaded speakers' presentations and summary videos to Figshare (their donation of time and space is much appreciated) - please email us if you'd like to receive the link. In the meantime, we invite you to share this newsletter with interested colleagues/contacts so that we can continue to develop our network of ambassadors for research transparency. Finally, we'd appreciate your feedback and ideas on the newsletter (and CBMRT's initiatives more broadly)... and don't forget to follow us on twitter @CBMRT_org.


Reproduced courtesy of Professor Philippe Ravaud