Open Science in Neuropsychiatry:

Mental Health and Dementia

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Introduction

Mental health problems and dementia are major and increasing causes of burden of disease. Progress has been made in developing treatments for some disorders although these were often discovered by serendipity or are based on theoretical psychological models. The efficacy of current psychological and pharmacological treatments is well established and worthwhile – and there is certainly no place for the scepticism and nihilism occasionally expressed. However it is true that no current treatments target known biology or modify a known disease process. Furthermore, and even more fundamentally, our diagnoses are based entirely on clinical symptoms and we have few reliable biomarkers.

These limitations of current knowledge fundamentally restrict our ability to diagnose reliably and early – or to provide treatments precisely targeted at biological abnormality. In some disorders, such as dementia, there are no currently available disease modifying treatments.

The presumed complexity of the biology of mental disorders, the challenges in standardising diagnosis and the lack of reliable biomarkers of disease or outcome are major barriers in treatment development. Further, it is likely that treatments aimed rationally at secondary prevention of disease will need to be given for many years to have the desired effect. Together, these factors conspire to produce a high risk of failure in treatment development. This high level of risk has increasingly discouraged pharmaceutical companies from developing novel therapies. Even if effective treatments are produced, the development process is long, leaving very little postmarketing patent life on which to generate return on investment. Protection of intellectual property has been paramount – resulting in little collaboration, and the use of various strategies to obtain competitive advantage. The absence of commercial interest produces a pessimistic view of the scientific tractability of mental disorders and dementia which then infects non-commercial funding (public and charitable funding). It is well known that funding for research in mental disorders and dementia lags behind disease areas which seem to offer greater chance or rapid therapeutic breakthrough and fails to reflect the global burden of disease. It can be persuasively argued that non-commercial funding is needed to de-risk commercial research and development – even better is when pre-competitive collaboration between commercial and non-commercial funders occurs because this potentially speeds the impact of advance into treatments for patients.

In this context, open science offers a model to build the interdisciplinary and collaborative networks that make optimum use of resources (including secondary analysis of existing datasets), facilitating reproduction and hence the reliability of science and speed of progress.

There are several areas where exemplars in open science are beginning to shape research in mental health and dementia:

1. Open sciences in the understanding of underpinning neurobiology: neuroimaging

Neuroimaging is a window into the living brain and is one of the most powerful tools available to clinical neuroscience. As a research modality, neuroimaging shares the need for open science to improve robustness, reproducibility, rigour and speed of progress [1]. The nature of neuroimaging data is such that an open science approach will bring some specific benefits that will transform the field from being one of much promise, to being able to properly deliver translational clinical research.

The common attributes of all neuroimaging modalities (MRI, PET, MEG etc) are that the data are resource intense to acquire (expensive equipment, several personnel involved, participants have to attend a facility for at least an hour), and the scanners produce large data files that require specialist knowledge and equipment to store and process. As a result, subject numbers have typically been small, which is particularly problematic for neuro-psychiatric research where individual diagnoses are often associated with heterogeneous presentations and multiple sub-types. Data sharing/pooling is an obvious way to increase statistical power, but even in situations where data custodians are willing and able to share data there are a number of technical barriers to overcome. For historical reasons most neuroimaging research data is 'siloed' in specialist imaging centres and processed using a wide range of software tools. Even within modality (e.g. MRI) the scanner manufacturers and software versions differ such that data harmonisation is a challenge. Over the last decade some important progress has been made towards development of data repositories [2], and data standards [3] and although imaging data has historically been difficult to share, some of the major analysis software developers have long used an open-source approach (e.g. FSL and SPM [4,5]. A new data sharing initiative that builds on this progress is taking shape as part of the UK MRC's Dementias Platform UK (http://www.dementiasplatform.uk/). We

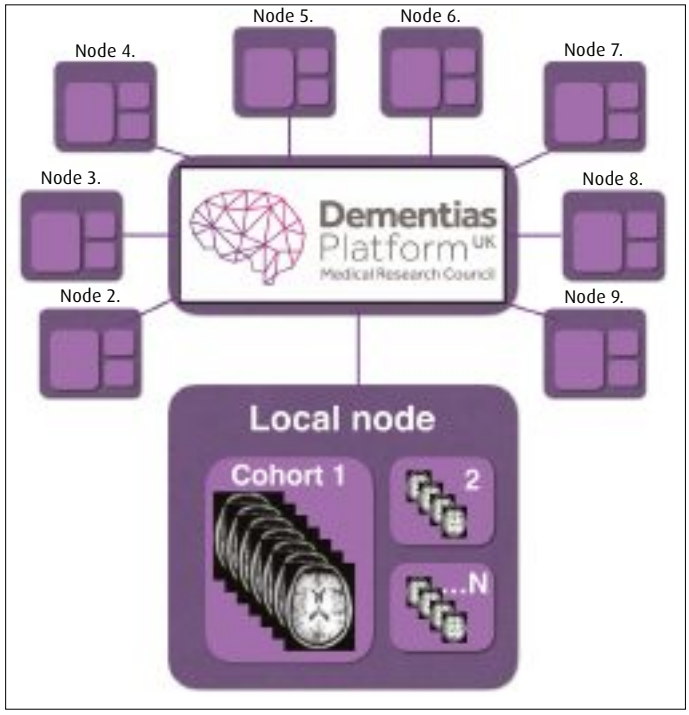

Figure 1. An example of federated data management across the imaging centres of the MRC Dementias Platform UK (info.dpuk.org). Cohort data are managed on local 'nodes' and are passed to the central hub for aggregation and sharing.

are building a federated infrastructure based on the XNAT technology to facilitate the sharing of neuroimaging data collected as part of dementia-relevant cohorts [5].

Data sharing challenges for neuroimaging are not specific to mental health, but are compounded by diagnostic complexity, and are particularly important to solve where the research modality holds such promise for elucidating the pathological mechanisms underlying these disorders and diseases of the brain.

2. Innovative drug development in neuropsychiatry: the new open science ecosystem

For all governments and most medical consumers – private or public, the cost of novel drug development is becoming unaffordable [6]. The direct (by illness) or indirect (support of patient by carers, families and friends) impact in economic productivity is escalating. Lifestyle and demographic changes, including a decrease in the relative proportion of carers in the coming decades, will exacerbate this crisis in healthcare as the incidence of long-term chronic diseases continues to increase. As the budgets for care provision come under ever more intense strain, with an increasing percentage of GDP devoted to healthcare in western economies, the crisis in healthcare will grow while the pharmaceutical industry continues to downsize across the World, shutting major research sites and laying off tens of thousands of trained professionals [7]. Furthermore, growing competition in research and marketing activities in lower cost countries with growing economies, such as China, India, and Brazil, have driven the pharmaceutical industry to focus on lower risk activities - at the expense of reducing efforts in difficult but crucial areas such as psychiatry. In desperation, different groups have aggressively acquired late stage, perceived "de-risked assets" across the entire industry [8], thus further exacerbating the depletion of the talent and innovation pool. Given their rates of failure and extended research timelines, pioneer medicines and complex diseases demand substantial innovations in the way we organise the relationships of the multiple stakeholders involved in drug discovery.

Due mainly to the reasons outlined above (limited understanding of biology, lack of validated biomarkers and animal models) failure rates in neuropsychiatry for pioneer targets in Phase II are in excess of 95% [9]. This is primarily because our understanding of many chronic diseases is poor. This complexity, coupled with the plethora of potential biological targets arising from genomic research, makes selection of the best drug target a significant challenge. Furthermore, massive duplication of effort, due to secrecy fuelled by outdated patenting strategies in both the drug discovery industry and academia effectively reduces the number of drug targets and hypothesis we can efficiently test with finite global public and private investments [10]. In fact, left unattended, we believe the ill-considered use of resources under the prevailing secrecy model will ultimately undermine the legitimacy of public investments in healthcare research as it fails to bring clear real benefit to the society (e.g. the failed promises of delivering transformational therapies after the completion of the Human Genome Project in 2003).

Recently, several open source pre-competitive public-private partnerships have catalysed discoveries in pioneer, high-risk areas of early-stage drug discovery. In the area of neuro-psychiatry, emerging initiatives are aiming at more efficient structuring of early- and late-stage discovery platforms, with a strong emphasis on the open science [11, 12]. This is further reinforced by a recent report from the NY Academy of Science [13] recommending the adoption of open, pre-competitive initiatives to accelerate the rate of discoveries.

Another example of open initiatives working on neuro-psychiatry is the Structural Genomics Consortium (SGC). Formed in 2004, it has continually and successfully challenged the established pre-competitive limits by generating high-value scientific assets, including novel chemical compounds and placing all in the public domain, in the absence of patents and other forms of intellectual property [14]. This has enabled an unprecedented acceleration in discoveries of new drug targets, backed by robust, reproducible and diversified data, and culminating in pioneer clinical trials in less than three years – compared to the typical range of 6-30 years observed in the closed model [15], and at a minimal fraction of the usual investment. Some preliminary studies have analysed the SGC's model although most are narrowly focused in more immediate aspects, such as increases in industrial productivity [16].

3. Transparency about treatment effects: open access to trial data

The World Health Organization, the Nordic Trial Alliance and the US Institute of Medicine recently called for a transformation of existing scientific culture to one where "data sharing is the expected norm." [17]. In this context, the efforts of industry, too, should be acknowledged (see the GlaxoSmithKline's leadership on data disclosure efforts - see www.clinicalstudydatarequest.com/). The call has also included the publication of clinical trial data on patient level. The process of opening access to clinical trial data has now been delayed for a series of reasons – this delay will have negative consequences for medical research and patients' outcomes.

Clinical trials are the best scientific investigations we have to assess the effects of interventions in patients. Hundreds of thousands of people worldwide have agreed to participate in a randomised controlled trial aiming to find out better treatments for their disorders and, ultimately, help the progress of medical science. According to the Declaration of Helsinki, all investigators carrying out a clinical trial should register the study protocol and report their results within a reasonable amount of time, ideally 12 months. Open access to clinical trial data provides the opportunity for validation/replication of the main results of a clinical study and the reuse of trial data for secondary research (i.e. systematic reviews and meta-analyses). Transparency carries some risks [18]. Patients' privacy must be guaranteed by adequate policy and technological measures (particularly in rare diseases where persons could potentially be identified), but at the same time confidential commercial information should be protected to avoid inappropriate use of data, which can discour-

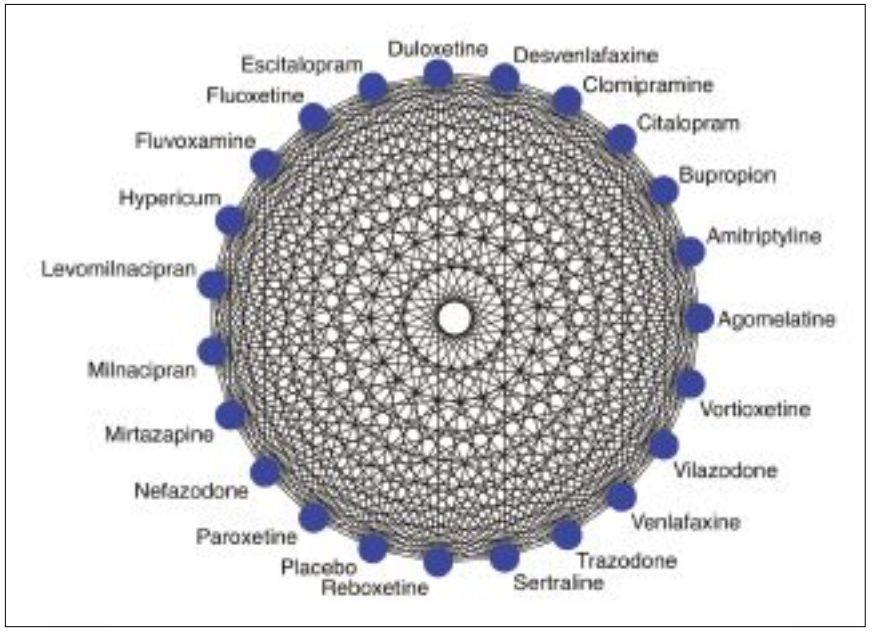

Figure 2. Hypothetical network of all possible pairwise comparisons between licensed antidepressants. The blue nodes represent the number of randomised participants (sample size) and the black lines the number of trials comparing every pair of treatments.

age companies from investing further in drug development. Consent protocols agreed by regulatory agencies, pharmaceutical industry, journal editors, researchers from academia and patients' representatives, need developing to allow the reuse of data in an easy and open manner.

Across medicine, mental health is one of the fields that could benefit from open access to clinical trial data. Open access to clinical trial data will enable researchers to compete to properly answer the most relevant clinical questions. For instance, it would help clarify the extent to which psychotropic drugs work. Efficacy of pharmacological treatments used in psychiatry, most of all antidepressants, has been questioned many times and is still under investigation [19]. It is well known that studies with significant or positive results are more likely to be published than those with non-significant or negative results [20]. Having access to primary data from trials for re-analysis, independent researchers can increase the rigour of the evidence base. A recent paper showed that, in contrast with the original 2001 publication, which claimed to show that paroxetine was well tolerated and effective for major depression in adolescents, the re-analysis of the data from the same randomised trial concluded that the antidepressant was not more efficacious than placebo and reported serious adverse events in the active treatment group, including self-harm and suicidal ideation [21]. Publication bias can be prevented by prospective registration of trials and online registers of clinical trials list all the information about methods and results of completed trials. Since 2007, the Food and Drug Administration in the US requires that study results must be posted on ClinicalTrials.gov,within a year of the completion of the trial for all trials with at least one site in the US. So far only a fifth of trials registered on this database had reported results within one year [22].

Open access to data from clinical studies at the individual patient level make possible individual patient data meta-analyses (IPD MA), which allow more sophisticated statistical elaborations (like time-to-event and subgroup analyses), the combination of different scales of measurement at the single item level, and the in-depth exploration of the patient's factors that may affect treatment outcome [23]. An IPD-MA aimed at estimating the relative benefit of antidepressants in adults with major depression across the wide range of patients'

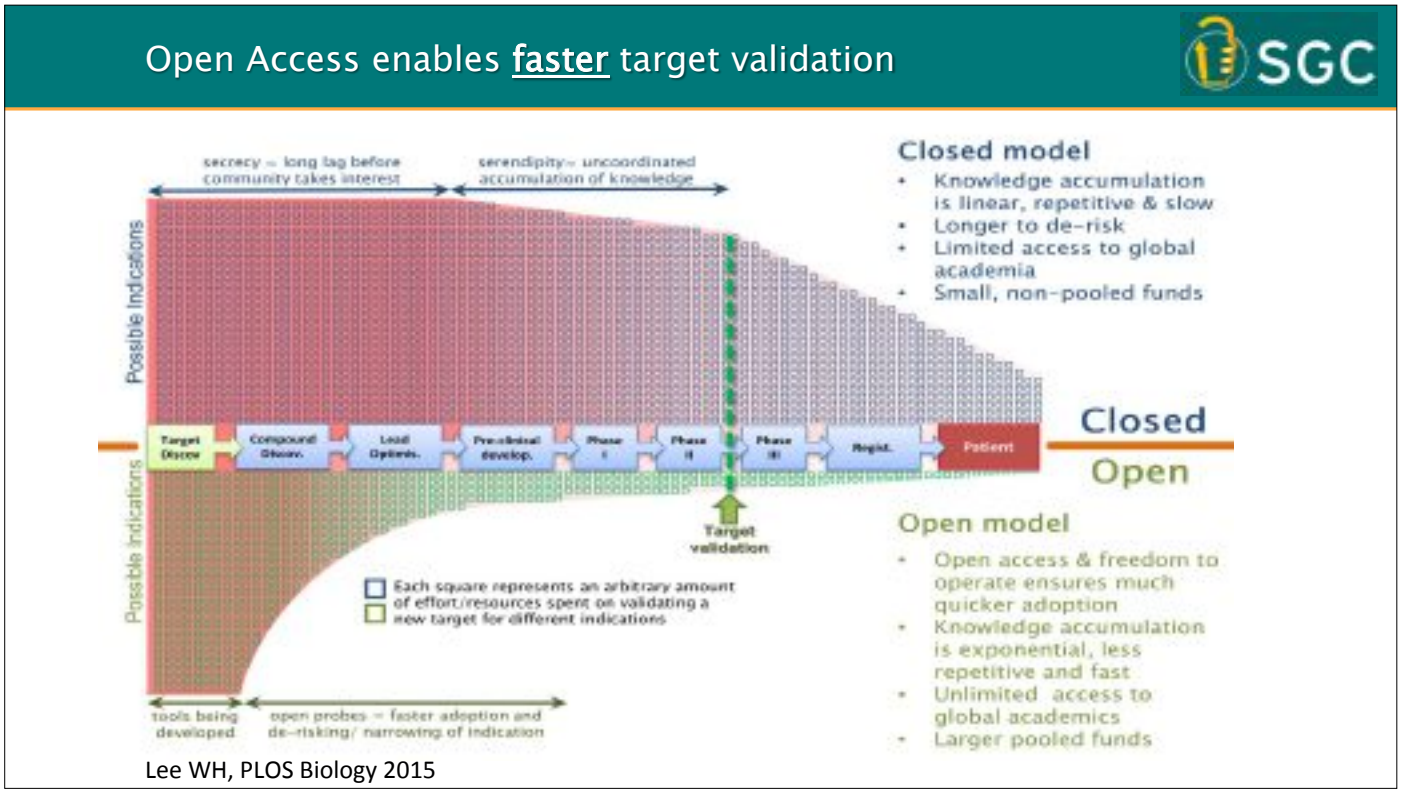

Figure 3. Open science accelerates identification of the best targets and drug indications, in the correct patient population. The Closed (upper half) model is compared to the Open (lower half) model; the availability of open access chemical tools for novel proteins and the freedom to operate enable the global community to explore different indications and diseases in parallel and quickly share back through publications. The breadth and depth of the studies in the open model lower the risks of failure in subsequent stages in a typical drug discovery programme, allowing the scientists to focus on the most promising indications, whilst reducing the level of effort (open squares), wastage, and duplication engendered by secrecy of the closed models.

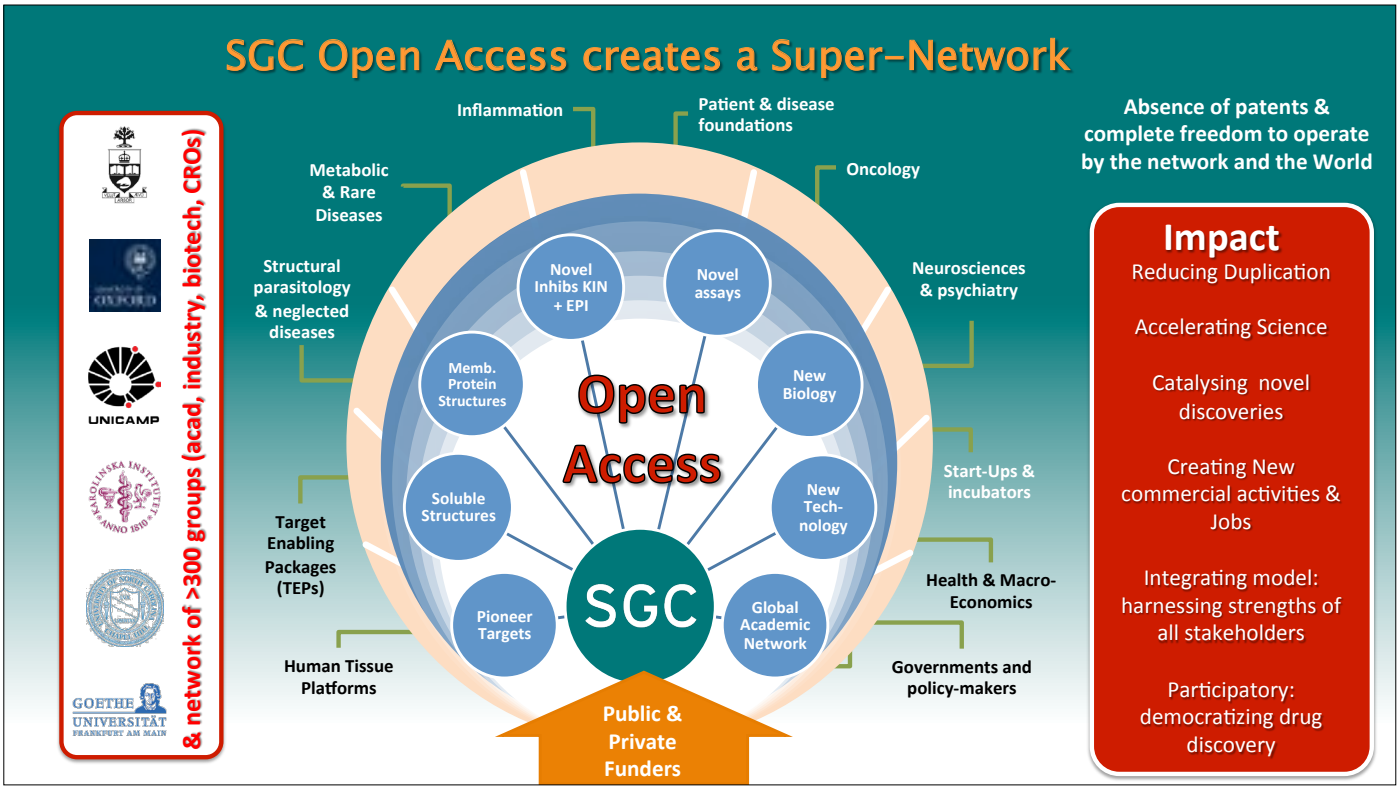

Figure 4. Open science breaks down barriers, creating a more inclusive and innovative ecosystem. Alongside generating novel biology and research tools open science initiatives such as the one adopted by the SGC naturally attracts new interdisciplinary and cross-sector stakeholders keen on breaking down barriers to create breakthrough innovation.

baseline severity of symptoms [24]. found that the magnitude of benefit of antidepressants compared with placebo increased with severity of depression symptoms, being minimal or non-existent on average in patients with mild or moderate symptoms, but substantial for patients with severe depression.

A methodologically sound systematic review and meta-analysis requires full access to clinical study data. This is true for both pharmacological and psychological interventions [25]. Data from published trial reports are becoming increasingly inadequate for addressing important questions in a thorough and unbiased way. Whereas evidence synthesis methodology has and will continue to develop in the future, new barriers to progress are in sight, such as data protection laws or price tags being attached to the data, which need to be tackled soon and globally. Campaigns, like the AllTrials initiative, call for all past and present clinical trials to be registered and their full methods and summary results reported (http://www.alltrials.net/find-out-more/all-trials/). Action is urgently required to ensure that the combined experience and data from thousands of clinical trials about commonly used treatments is not lost.

REFERENCES

1 Schwartz Y et al. PyXNAT: XNAT in Python. Front Neuroinform 2012;6:12.

2 Eickhoff S et al. Sharing the wealth: Neuroimaging data repositories. Neuroimage. 2016;124(Pt B):1065-8.

3 Gorgolewski KJ et al. The Brain Imaging Data Structure: a standard for organizing and describing outputs of neuroimaging experiments. bioRxiv 2016. doi: http://dx.doi.org/10.1101/034561

4 Smith SM et al. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage 2004;23 Suppl 1:S208-19.

5 Ashburner J. SPM: a history. Neuroimage 2012;62(2):791-800.

6 Herrick R et al. XNAT Central: Open sourcing imaging research data. Neuroimage 2016;124(Pt B):1093-6.

7 Munos B. The Ugly Cost Of Developing New Drugs -- Can We Make It Prettier? Forbes. 2014 http://www.forbes.com/sites/bernardmunos/2014/11/20/the-ugly-cost-of-developing-new-drugs-can-we-make-it-prettier/#cbf3af163f4f

8 Herper M. A Decade In Drug Industry Layoffs. Forbes. 2011

9 Bunnage ME. Getting pharmaceutical R&D back on target. Nat Chem Biol. 2011;7(6):335-9.

10 Cook et al. Lessons learned from the fate of AstraZeneca's drug pipeline: a five-dimensional framework. Nat Rev Drug Discov. 2014;13(6):419-31.

11 Edwards AM, et al. Too many roads not taken. Nature. 2011;470(7333):163-5..

12 Norman T, et al. The Precompetitive Space: Time to Move the Yardsticks. 2011;3(76):76cm10. doi: 10.1126/scitranslmed.3002399.

13 NY Academy of Science. Alzheimer's Disease Summit: Path to 2025 . 2013

14 Lee WH. Open access target validation is a more efficient way to accelerate drug discovery. PLoS Biol. 2015;13(6):e1002164.

15 Knapp S, Sundstrom M. Recently targeted kinases and their inhibitors-the path to clinical trials. Curr Opin Pharmacol. 2014;17:58-63.

16 Marcello R, Executing an open innovation model: Cooperation is key to competition for biopharmaceutical companies. Deloitte, 2015

17 Loder E, Groves T. The BMJ requires data sharing on request for all trials. BMJ 2015;350:h2373.

18 Bonini S, Transparency and the European Medicines Agency--sharing of clinical trial data. N Engl J Med 2014;371(26):2452-5.

19 Cipriani A, Geddes JR. Placebo for depression: we need to improve the quality of scientific information but also reject too simplistic approaches or ideological nihilism. BMC Med 2014;12:105.

20 Song F, Dissemination and publication of research findings: an updated review of related biases. Health Technol Assess. 2010 Feb;14(8):iii, ix-xi, 1-193.

21 Le Noury J, Restoring Study 329: efficacy and harms of paroxetine and imipramine in treatment of major depression in adolescence. BMJ 2015;351:h4320.

22 Prayle AP, Compliance with mandatory reporting of clinical trial results on ClinicalTrials.gov: cross sectional study. BMJ 2012;344:d7373.

23 Stewart LA, Tierney JF. To IPD or not to IPD? Advantages and disadvantages of systematic reviews using individual patient data. Eval Health Prof 2002;25:76-97.

24 Fournier JC, Antidepressant drug effects and depression severity: a patient-level meta-analysis. JAMA 2010;303:47-53.

25 Coronado-Montoya S, Reporting of Positive Results in Randomized Controlled Trials of Mindfulness-Based Mental Health Interventions. PLoS One. 2016 11(4):e0153220.

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