

Disclosure of individual-patient data: time to put the patient first

The International Committee of Medical Journal Editors (ICMJE) proposes that authors reporting clinical trials in member journals will be required to share the underlying de-identified individual-patient data with others (Taichman *et al.*, 2016). This proposal has the potential to strengthen trust in the clinical research endeavour, or to damage it. The ICMJE has a duty to provide clear guidance on best practice for data sharing to investigators and authors around the world. We believe that such guidance should prioritize the unique needs of the patients who take part in clinical research, on whose participation and trust medical progress depends. There can be no choice between good science and ethical science – good science must be ethical above all else.

Here, we make seven recommendations.

1. We believe that uncontrolled public access to individual-patient data is unethical, so the ICMJE should make it clear that data sharing needs to be restricted to research purposes only

We owe participants in clinical research the certainty that their data will be shared only for research purposes. Shared individual-patient data are, however, being accessed by law firms, lay media and the general public. Major research funders and sponsors in academia and industry have invested in controlling access to individual-patient data so that it is used only for research. Many other institutions are likely to require incentives from the ICMJE if they are to make individual-patient data available for research in an ethical and acceptable way.

We owe participants in clinical research the certainty that their data will be shared only for research purposes. Anything else is unethical. The Declaration of Helsinki states that medical research participants “must be adequately informed of the aims, methods, sources of funding [and]... conflicts of interest [and] institutional affiliations of the researcher,” as well as the anticipated benefits and potential risks of the study (World Medical Association, 2013). Available information on patient views about sharing of individual-patient data comes from a single study, and a wealth of studies of potential and actual contributors to repositories that store biological samples for use in research (biobanks). The former suggested that research participants and their families consider sharing of individual-patient data acceptable for

scientific purposes and to promote health, but are concerned about the media accessing and misinterpreting or misrepresenting their data (Merson *et al.*, 2015). A recent systematic review of the latter concluded that patients contributing to biobanks expect to be informed of the broad aims of the research in which these biobanks participate (Husedzinovic *et al.*, 2015). Contributing patients are concerned about the data being used for non-research purposes that might restrict their access to health insurance, employment and/or medical care, or cause stigmatization. Accordingly, contributors to biobanks are less willing for researchers to share their data with commercial enterprises and government institutions than with other academic researchers (Garrison *et al.*, 2015).

Shared individual-patient data are, however, being accessed by law firms, lay media and the general public. Since 2010, the European Medicines Agency has enabled interested parties to request data from clinical trials of medicinal products that have been submitted for marketing authorization. Of 191 requests for clinical trial data made to the European Medicines Agency between 2010 and 2013, only 17.8% came from academic or research institutions and 9.4% from healthcare professionals; a further 26.7% came from the pharmaceutical industry (Bonini *et al.*, 2014). Even if all of these requests were for the purposes of research, almost half (46.1%) of all data requests were most likely not for research, but rather from law firms (15.7%), lay media (11.0%), consultants (7.9%) and the general public (5.2%), as well as governmental and non-governmental organizations. As described above, sharing individual-patient data with groups who are probably not intending to use them for research is unlikely to be considered ethical or acceptable by research participants.

Major research funders and sponsors in academia and industry have invested in controlling access to individual-patient data so that it is used only for research (Hopkins *et al.*, 2016; Krumholz *et al.*, 2014; Navar *et al.*, 2016; Strom *et al.*, 2014; Sydes *et al.*, 2015; Tudur Smith *et al.*, 2015). Platforms such as ClinicalStudyDataRequest.com help to manage access to study data generated by multiple pharmaceutical companies, with requests for data typically being reviewed by an independent review panel (Krumholz *et al.*, 2014). A controlled access approach has not unduly restricted the availability of data for research purposes; so far, over 90% of requests for individual-patient data made through such platforms have been approved (Table 1). A controlled access approach to data sharing is also preferred by a substantial minority of prospective biobank participants (McGuire *et al.*, 2011).

Table 1. The proportion of requests for individual-patient data that have been approved by the independent review board responsible for different data sharing platforms.

Reference	Data source	Period	Requests approved/all decisions (%)
Strom <i>et al.</i> (2014)	ClinicalStudyDataRequest.com	May 2013–May 2014	36/39 (92.3%)
Navar <i>et al.</i> (2016)	ClinicalStudyDataRequest.com, the Yale University Open Data Access Project (YODA) and the Supporting Open Access for Researchers (SOAR) initiative	2013–2015	154/166 (92.8%)
Doshi and Jefferson (2016)	Requests to the European Medicines Agency by two researchers/journalists	2011–2015	11/12 (91.7%)
Sydes <i>et al.</i> (2015)	UK Medical Research Council Clinical Trials Unit	2012–2014	80/84 (95.2%)

Many institutions are likely to require incentives from the ICMJE if they are to make individual-patient data available for research in an ethical and acceptable way. Currently, the costs of data sharing are borne by those who generate the data, rather than those who use them (Institute of Medicine, 2015). Institutions around the world may favour unrestricted public release of individual-patient data simply to avoid the additional costs involved in a controlled access approach, which include setting up or joining a data sharing site and independent review panel. To provide sufficient incentive, the ICMJE must insist on a controlled approach to data sharing as a precondition for publication of clinical trials in member journals.

2. We believe that multiple analyses of individual-patient data have the potential to distort the evidence-base, so the ICMJE should insist on registration and disclosure of all analyses

Multiple analyses of individual-patient data have the potential to bias the medical literature. The ICMJE should require analyses of shared individual-patient data to be prospectively registered in a public database. ICMJE member journals should actively support dissemination of such analyses.

Multiple analyses of individual-patient data have the potential to bias the medical literature (Koenig *et al.*, 2015). Analyses of individual-patient data may lead to biased results in two ways. First, the design of the new analysis (e.g. selection of endpoints and time points) may be influenced (biased) by the investigators' reaction to the results of the original analysis (or other early analyses of shared data); currently, fewer than 5% of analyses of shared data seek to replicate the original analysis as pre-specified by the data originators (Navar *et al.*, 2016; Sydes *et al.*, 2015). Secondly, conducting many analyses makes it likely that a false result will emerge by chance alone (Schulz and Grimes, 2005a; Schulz and Grimes, 2005b). If investigators undertake many analyses but report only the significant or surprising findings, the medical literature will be distorted by publication bias. Of four replication analyses conducted using data from ClinicalStudyDataRequest.com, the Yale University Open Data Access Project (YODA) or the Supporting Open Access for Researchers (SOAR) initiative between 2013 and 2015, the only one to be published reached a different conclusion from the original analysis (Navar *et al.*, 2016).

The ICMJE should require analyses of shared individual-patient data to be prospectively registered in a public database, in the same way that it requires the original study to be registered (De Angelis *et al.*, 2004). Prospective registration of planned and ongoing analyses will provide the same benefits as prospective registration of clinical trials: minimizing duplication in research, facilitating follow-up to encourage publication and enabling measurement of publication bias. Such benefits are contingent on knowing that registration is truly prospective, and only a controlled access approach to data sharing will enable investigators to verify that registration occurred before the analysis commenced.

ICMJE member journals should actively support dissemination of analyses of individual-patient data. To minimize publication bias, it will be important for member journals to publish new analyses whether or not they reach the same conclusions as the original analysis. The ICMJE can also call on independent review boards to insist on a commitment to publish results before data are shared. Exposing research participants to the risk of data sharing is unethical unless the chances of patient benefit are maximized through sound scientific methodology.

3. We believe that the patient perspective has been largely ignored, so the ICMJE should call for this perspective to be better studied and taken into account

Surprisingly little is known about what participants in clinical research want and need from sharing of individual-patient data. The ICMJE needs to acknowledge that our lack of understanding of the patient perspective is cause for concern, and to call for it to be better researched. The ICMJE should also recommend practical steps for involving research participants in the sharing of individual-patient data.

*Surprisingly little is known about what participants in clinical research want and need from sharing of individual-patient data. This is cause for concern for all who believe that clinical research should be undertaken collaboratively with patients. We need to recognize that there is conflict between the interests of different stakeholders involved in the generation and sharing of clinical trial data. Patient voices need to be heard. Involvement of a patient representative as a co-author of the landmark Institute of Medicine report is welcome, but the views of patients are not all the same. Not only does the scientific community not know patients' views on the issue of data sharing, it does not appear to be interested in understanding them; rather, studies of stakeholder perspectives over the past 20 years have focused on the needs and desires of researchers in academia and industry, and the views of journal editors (Hopkins *et al.*, 2016; Kirwan, 1997; Rathi *et al.*, 2012; Rathi *et al.*, 2014; Reidpath and Allotey, 2001; Saunders *et al.*, 2014; Sturges *et al.*, 2015; Tudur Smith *et al.*, 2014). We were able to identify only one study reporting participants' attitudes to data sharing (Merson *et al.*, 2015), though the fact that it was published last year may indicate the beginning of a process of patient engagement. Until further studies have been conducted, we*

will need to rely on extrapolation of the results of studies of potential and actual participants in biobanks (Garrison *et al.*, 2015; Husedzinovic *et al.*, 2015).

The ICMJE needs to acknowledge that our lack of understanding of the patient perspective is cause for concern, and to call for it to be better researched. Populations worthy of particular focus include children (including whether there is the need for re-consent for data sharing once participants reach adulthood), minorities and patients with rare diseases or diseases associated with stigma. Implementing potentially irreversible policy changes is unethical without listening to the views of all stakeholders, particularly those with the least power.

The ICMJE should also recommend practical steps for involving research participants in the sharing of individual-patient data. Such steps include inviting patient participants to be members of the independent review panels that approve requests for data sharing.

4. We believe that no method of de-identification is absolute and ‘future-proof’, so the ICMJE should make it clear that sharing of individual-patient data must be restricted to the minimum necessary

There are no uniform international standards for determining when data have been sufficiently anonymized or de-identified for them to be shared. Lack of clarity about appropriate levels of de-identification has led to public release of routine medical data that have allowed patients to be re-identified. Although we are not aware of any clinical trial participants who have been re-identified from their individual-patient data, the same principles are likely to apply. Re-identification now or in the future is an important risk to research participants because it leads to their identity being matched with health information that should remain confidential. The ICMJE should require investigators to minimize the risk of re-identification through a controlled access approach that minimizes the sharing of individual-patient data.

There are no uniform international standards for determining when data have been sufficiently anonymized or de-identified for them to be shared (Institute of Medicine, 2015). Indeed, complete and ‘future-proof’ de-identification of individual patient data may not be possible. In our opinion, only pooling can truly achieve patient anonymity. When we remove someone’s name, address and identification number, we rely on it being too difficult to

identify the individual based on his or her other characteristics. However, whether an individual can be identified from data that are commonly recorded for clinical trials, such as age, sex/gender, ethnicity, location/study centre, height, weight, primary diagnosis, comorbidities and concomitant treatments, very much depends on how unusual they are. A 40-year-old man with Duchenne muscular dystrophy would not be difficult to identify, and neither would a Hispanic woman from a provincial northern European city who has schizophrenia. The level of difficulty also depends on the computing power available and how much information can be gleaned from other sources.

Lack of clarity about appropriate levels of de-identification has led to public release of routine medical data that have allowed patients to be re-identified (Ohm, 2010). The medical record of the then Governor of Massachusetts was identified by one researcher based on date of birth, sex and ZIP code (which, in the USA, covers a population of approximately 7500 individuals on average). In a separate study, information contained in newspaper stories about hospital visits in a single US state was sufficient to identify the matching health record 43% of the time (Sweeney, 2015).

Although we are not aware of any clinical trial participants who have been re-identified from their individual-patient data, the same principles are likely to apply. For instance, a car accident is a reportable adverse event in a clinical trial and could be cross-referenced manually or automatically against details in a news article to establish a patient's identity. When we take into account the likelihood that future studies will involve whole genome sequencing, and that surnames can already be inferred from publicly available Y-chromosome sequences (Gymrek *et al.*, 2013), re-identification now or in the future is an important risk. Given the doubling in computing power every 2 years (Robison, 2012), plus a pace of technological change that sees transformative technologies, such as smartphones and the Internet, adopted around the world in decades rather than centuries, we simply cannot predict how data might be used to identify people in future. Yet once data have been released on the Internet without controls, they can be copied and shared indefinitely, and are, therefore, impossible to retrieve.

Re-identification now or in the future is an important risk to research participants because it leads to their identity being matched with health information that should remain confidential. Re-identification, whether by family, friends, employers, insurers, governments or criminals,

may be a particular concern for people with diseases still associated with stigma (e.g. mental, sexual or reproductive health issues, including depression, sexually transmitted diseases, sexual dysfunction and abortion) (Institute of Medicine, 2015). As Paul Ohm argues, “For almost every person on earth, there is at least one fact about them stored in a computer database that an adversary could use to blackmail, discriminate against, harass, or steal the identity of him or her,” and many of these facts may be health-related (Ohm, 2010). For people who are or who become well-known, by choice or as a victim of circumstance, the risks are particularly pronounced.

*The ICMJE should require investigators to minimize the risk of re-identification through a controlled access approach that minimizes the sharing of individual-patient data. Sharing individual-patient data more widely than required for the purposes of research is unethical. Given the potential for a catastrophic loss of public trust in medical research, release of individual-patient data should be controlled in the following ways. First, data sharing should be restricted to researchers seeking to answer a clearly defined research question. Secondly, only the minimum data required to answer the research question should be released. Thirdly, data use agreements should require researchers to use data only for the purposes of the agreed research and not to seek to re-identify participants. Fourthly, data use agreements should specify requirements for data security and audit (who has accessed which data, when and why) (Harman *et al.*, 2012). Fifthly, in line with patient expectation (Husedzinovic *et al.*, 2015), data use agreements should specify the sanctions to be taken if the preceding terms are broken. These principles should be endorsed by the ICMJE.*

5. We believe that current informed consent is inadequate, so the ICMJE should clarify what is required for genuinely informed consent

Current approaches to informed consent do not fully disclose the risks associated with sharing of individual-patient data. The ICMJE needs to make it clear that a new approach to informed consent is needed.

Current approaches to informed consent do not fully disclose the risks associated with sharing of individual-patient data. We have not been able to identify studies of informed consent to data sharing as part of a clinical trial. Again, insight comes from studies of potential participants in biobanks. Among these, a randomized study has shed important light

on the inadequacy of existing approaches to informed consent (McGuire *et al.*, 2011). Participants were randomized to three forms of consent, debriefed and given the chance to change their choice. Before debriefing, 83.9% of participants consented to uncontrolled public data release. After debriefing, 53.1% chose public data release, 33.1% chose controlled release and 13.7% opted out of data sharing. The fact that, once appropriately informed, almost half of the participants opted out of uncontrolled data release implies that their original consent was not truly informed. In another study, over two-thirds of prospective contributors to a biobank said that it was important to know about privacy risks and large-scale data sharing when deciding whether to contribute to a biobank (Beskow *et al.*, 2010). Of 29 statements included in a model consent form, those relevant to privacy risks and large-scale data sharing were rated second and equal third in importance.

- ‘There is a risk that someone could get access to the data we have stored about you’ (selected as important by 71% of potential participants, making it the second most important of 29 statements)
- ‘Your name and other information that could identify you will never be released into a scientific database’ (69%, third equal in importance)
- ‘Nobody will know just from looking at a database that the information belongs to you’ (69%, third equal in importance).

The following statement was ranked first in importance by potential participants.

- ‘We will offer to tell you a finding like this [individual results from research done using your sample] only if it is about a disease that is likely to cause early death if not treated’ (73%).

As discussed below, statements such as ‘Nobody will know just from looking at a database that the information belongs to you’ and ‘Your name and other information that could identify you will never be released into a scientific database’ may not be accurate.

The ICMJE needs to make clear that a new approach to informed consent is needed. Consent can be truly informed only if participants consider and understand the potential implications of their decision. In the case of uncontrolled data sharing, this means agreeing to making personal data available to anyone in the world, at any future time, for any purpose – even potentially including re-identification, aggregation and sale. It is difficult to understand how such consent can ever be truly informed, even in adults with full mental capacity. Such consent becomes particularly problematic for those with limited mental capacity (including those with developmental disorders and dementia) and children; indeed, there may need to be

mechanisms for children to provide consent themselves once they reach adulthood. Even with controlled data sharing, re-identification remains an issue, and assessment of risk may need to be individualized based on patient characteristics. Research participants may also need to be warned that, if they access their own data, they may learn about prognostic factors that could influence their ability to obtain health or life insurance.

6. We believe that patients deserve to have access to the data they help to generate, so ICMJE member journals should make a patient summary of results freely available

An important reason why patients take part in research is to find out the results. However, patients are not routinely provided with a summary of the results of the trial in which they took part. The ICMJE should require every clinical trial reported in a member journal to have a patient summary of results made freely available, without the need for registration or payment. Research participants may also want to see their own individual-patient data, and the ICMJE should call for further research in this area.

An important reason why patients take part in research is to find out the results. In a large US study, most patients said that they wanted to be informed about research findings, and that not being informed would make them less likely to participate in future clinical trials (Sood et al., 2009).

However, patients are not routinely provided with a summary of the results of the trial in which they took part (Wicks et al., 2014), and there are multiple barriers to them finding out about the results themselves. First, they are unlikely to be trained in how to identify a specific study in a literature database. Secondly, they may not be able to access the full text without registration and payment. Thirdly, they may not find the text fully comprehensible. We believe that failure to share clinical trial data with the patients who took part is unethical.

The ICMJE should require every clinical trial reported in a member journal to have a patient summary of results made freely available without the need for registration or payment. By integrating an aspect of data sharing that generates benefits for research participants themselves, it will be demonstrated that transparency can be for patients as well as about them.

Research participants may also want to see their own individual-patient data, and the ICMJE should call for further research in this area. Two recent studies have shown that most participants would like to be unblinded once a trial is complete (Armstrong *et al.*, 2013; Tajima *et al.*, 2013). It is possible that the promise of unblinding at the end of a trial may reduce the risk of patients unblinding themselves during a trial via social media (Wicks *et al.*, 2014). As well as treatment allocation, trial participants may be interested in accessing information collected on their health, particularly prognostic information. Again, studies of biobank participants provide useful information. In one study, most biobank participants wished to be informed about all their health-related genetic risks, even the risks of diseases without known prevention or treatment (Bui *et al.*, 2014). There is particular interest among participants enrolled in studies of prodromal Alzheimer’s disease in learning about their prognosis (Facio *et al.*, 2013; Gooblar *et al.*, 2015; Grill *et al.*, 2013). Some researchers are already developing processes for identifying which participants would appreciate such information and how they should be informed (Harkins *et al.*, 2015). Careful thought is required, however, as few research participants feel well informed about the implications of genome sequencing for their own or their family members’ health and insurability, and US laws that prohibit employment and insurance discrimination based on genetic status do not apply to important biomarkers such as amyloid for neurodegenerative diseases (Arias and Karlawish, 2014).

7. We believe that both the benefits and risks of data sharing are poorly characterized, so the ICMJE should call on researchers to measure both intended and unintended consequences and review its policy accordingly

The research community needs to measure the intended and unintended consequences of mandatory data sharing, including the costs. The ICMJE should review its policy once the benefits and risks of data sharing have become clear.

The research community needs to measure the intended and unintended consequences of mandatory data sharing, including the costs. The intended benefits of data sharing can be assessed in several ways. First, the number of studies using shared individual-patient data for different purposes (e.g. replication, meta-analysis or hypothesis generation) can be assessed. So far, the level of use of shared individual-patient data has been surprisingly limited (Navar

et al., 2016). We hope that recent guidance will increase the use of individual-patient data for replication and meta-analysis (Tierney *et al.*, 2015). Secondly, the downstream benefits of such analyses can be measured, for example, through their impact on treatment guidelines. Potential harm from data sharing can be assessed by measuring the impact of informed consent on recruitment rates in clinical trials. In a multinational study, privacy and confidentiality were the biggest concerns about participating in clinical research for nearly 20% of patients in the US, but fewer than 5% of patients in China (Wu *et al.*, 2015). In another study, over two-thirds of prospective participants in a biobank said that it was important to know about privacy risks and large-scale data sharing when make a decision about taking part (Beskow *et al.*, 2010). When properly informed, up to 20% of prospective biobank participants do not consent to any form of data sharing (McGuire *et al.*, 2011). If concern about data sharing reduces participation rates, the impact on the timeliness of research will need to be assessed. It will also be important to understand whether the participation of certain groups is particularly affected; for example, concern about disclosure of HIV status might be a barrier to clinical trial participation (Bass *et al.*, 2016). Any intervention that selectively excludes certain groups also has important implications for the external validity of clinical trials (Bauchner *et al.*, 2016). The costs of data sharing, which must be substantial, are currently largely unreported (Institute of Medicine, 2015). Further research is, therefore, needed.

The ICMJE should review its policy once the benefits and risks of data sharing have become clear. One key desired outcome of the ICMJE policy is trust in the clinical research endeavour, which should be strengthened and not damaged. In addition to the changes to the policy that we have recommended above, measuring the impact of the policy after implementation will enable changes to be made that maximize benefits and minimize risks.

8. Conclusion

In conclusion, unrestricted data sharing transfers risk from the research community to research participants, and that risk to participants has been insufficiently debated, understood and communicated. Patients who take part in clinical research are likely to be supportive of data sharing for research purposes but to be concerned about loss of privacy and data being used in ways that damage their interests. Individual-patient data that are shared on an uncontrolled basis are accessed by the general public and the media as well as by researchers, and such wide access and use is not consistent with the requirements of the Declaration of

Helsinki. De-identification is still an uncertain art, and it is impossible to predict how re-identification techniques will develop in future. Current levels of participant consent may not be sufficiently informed.

Much can be learned from the care.data fiasco in the UK. Following a thoughtful report from the Caldicott committee, the UK government agreed seven sensible principles for sharing individual data within the healthcare system (Department of Health, 2003). Over a decade later, care.data proposals to share individual patients' primary care medical records were announced with minimal consultation and communication (Hays and Daker-White, 2015). The backlash against care.data has put back the cause of medical research in the UK. At least there is clarity about the legal framework for data sharing in the UK but, on a global scale, it is not clear who is responsible or who should regulate access to patient data and how.

The ICMJE proposal risks doing a great deal of harm by prompting a flood of individual-patient data into the public domain without appropriate access controls. As the Declaration of Helsinki states, "While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects." We believe that individual-patient data should only ever be made available on a controlled basis, specifically for medical research, and that the ICMJE has a duty to make this clear.

9. Disclosures

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