

Regulatory Public Disclosure

COVID-19: Out there in all its glory

SECTION EDITOR

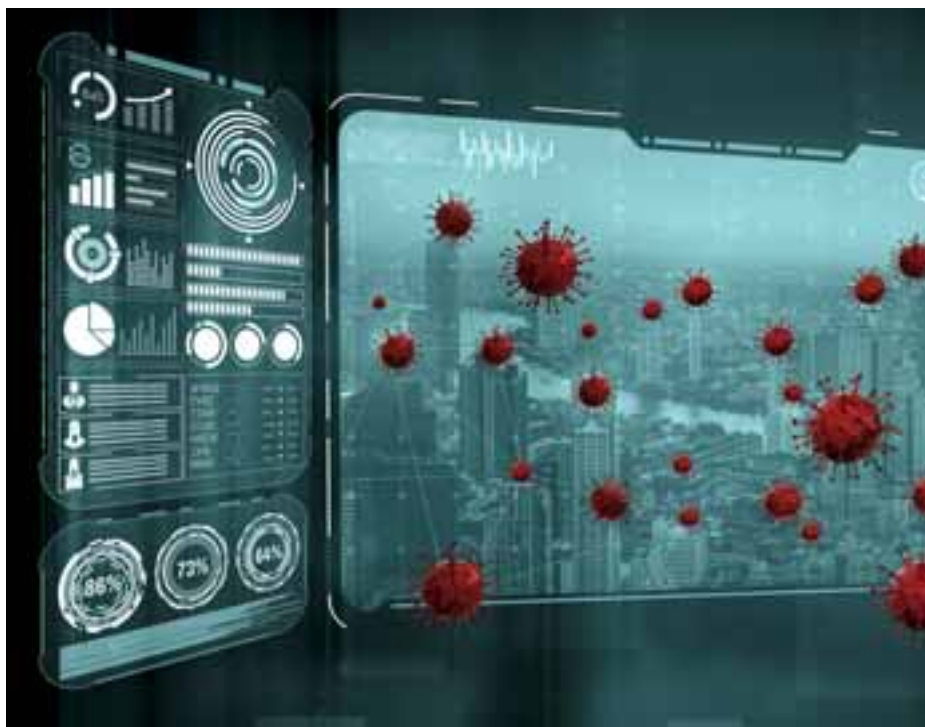


Sam Hamilton

sam@samhamiltonmwservices.co.uk

Editorial

In the first half of 2021, keeping up with the regional regulators' activities on COVID-19 medicines became a competitive sport. FDA's Emergency Use Authorizations (EUAs), EMA's Conditional Marketing Authorisations, and Health Canada's Interim Orders kept us all busy – if not doing, then reading. By late May 2021, the EU had approved remdesivir; conditionally approved two mRNA vaccines (Pfizer-BioNTech's and Moderna's) and two adenovirus vector vaccines (AstraZeneca's and Janssen's); had publicly disclosed the clinical documentation for the Moderna and Pfizer-BioNTech vaccines; and had endorsed dexamethasone. The EU had a further four vaccines under rolling review. The FDA had authorised the Moderna, J&J, and Pfizer-BioNTech vaccines under emergency use, as well as several medicines including monoclonal antibodies and remdesivir. Health Canada had "authorised with conditions" the Moderna and Pfizer-BioNTech vaccines under an Interim Order and had publicly disclosed the associated clinical documentation. Exhausted? Yes, weren't we all? Then some country agencies expedited access for their citizens even ahead of the regional regulators making their decisions. More COVID-19 vaccines and medicines are in development, and regulatory rolling review is now a commonly employed tool. All of this speaks of a highly regulated pharmaceutical industry, being pragmatic, responsive, and committed to finding operational and regulatory solutions to fast-track COVID-19 prophylactics and therapeutics in impossibly short timeframes! With the ability to use CRISPR technology to modify and re-code RNA vaccines in response to emerging viral variants, customised vaccines may be developed in a matter of weeks, scaled-up, and deployed. This can be considered conceptually similar to minor modifications in drug formulation, as would be represented in an Amendment to the New Drug Application for an already-approved drug. Regulators will need to maintain creativity and impetus to authorise vaccine variants as fast as we need them. All of this is playing out in a very public arena. Everyone has an opinion on what we do and how we do it. The source clinical study documentation provides the most objective information available; at least some is publicly accessible at EMA's Treatments



and vaccines for COVID-19 pages (<https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/conditional-marketing-authorisation>) and at Health Canada's Clinical Information Portal (<https://clinical-information.canada.ca/search/ci-rc>). A dedicated page titled "Transparency: exceptional measures for COVID-19 medicines" (<https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/transparency-exceptional-measures-covid-19-medicines>) clarifies how the transparency measures for a standard practice (i.e. non-COVID medicine) regulatory activity – such as scientific advice, rolling review, etc – stack up with that of the transparency measures for the same activity for a COVID-19 medicine. So for example, although publication of clinical trial data remains suspended for non-COVID medicines, COVID-19 data are published on the Clinical Data website: <https://clinicaldata.ema.europa.eu/web/cdp/home>. By the time you are reading this in print, there will undoubtedly be further updates – so the best advice is to watch this space and check these sites regularly. Through this pandemic, we are also really beginning to

understand the value of real-world data when combined with data collected through pre-approval pathways. Read more on this below.

This pandemic has also increased awareness of the importance of well-prepared and presented patient-facing documents. If we consent to participate in trials or receive a COVID-19 vaccine, we read some of this material as adult participants or patients ourselves. Children also need appropriately presented clinical trial documents – as Vidhi Vashisht and colleagues describe in their article on p. 52, "The ABCs of paediatric plain language summaries". This article provides guidance on plain language summary formats that appeal to children. All this reminds us of the need to keep patients centre-stage, as the UK Medicines and Healthcare Regulatory Agency (MHRA) plan to do in piloting a project that includes greater patient involvement in clinical trials and medicine development (<https://www.gov.uk/government/news/mhra-pilots-patient-involvement-in-new-applications>). Although at an exploratory stage, this initiative should serve patients better and increase transparency within clinical trials. It is certainly one to watch.

Sam Hamilton

Regulatory Public Disclosure Special Interest Group (RPD SIG) News

Visit the revamped RPD SIG page at: <https://www.emwa.org/sigs/regulatory-public-disclosure-sig/#>

Our current co-chairs are Holly Hanson and Tracy Farrow. A big “thank you” to Christopher Marshall for co-chairing with Tracy since the RPD SIG came into being in 2016; and a warm welcome to Holly who has kindly stepped up. We are delighted to introduce our newest committee member, Amanda Hunn. Amanda is a freelance consultant and subject matter expert on patient-facing documents, including the Patient Lay Summary (PLS), and brings valuable expertise through her previous experience as Head of Policy and Public Affairs at the Health Research Authority in the UK, where she led the EU-wide taskforce responsible for drafting the guidelines on writing lay summaries of clinical trial results on behalf of the European Commission and developing policy on informed consent including publishing joint guidance with the MHRA on eConsent. She sat on a national research ethics committee for 6 years and has co-authored a number of papers including “Guidelines for Inclusion of Patient-Reported Outcomes in Clinical Trial Protocols: The SPIRIT-PRO Extension”. Amanda shares her knowledge on the latest development in lay summaries. See the update on the next page on good lay summary practice.

EMWA's RPD SIG is interacting with Statisticians in the Pharmaceutical Industry (PSI) Data Transparency SIG (<https://www.psiweb.org/sigs-special-interest-groups/data-sharing-working-group>). This group shares experiences and challenges of external patient level data sharing, with particular focus on data privacy and anonymisation processes. Janice Branson and her colleagues first published their article “Secondary use of data – Unleashing Data Assets to Create Value” in the PSI publication *SPIN* in Spring 2021. In the article, which we are republishing here on p. 105 to share with the medical writing community, the authors describe the wider picture of data sharing in the pharma industry using examples of internal data re-use programmes. Please do not hesitate to provide feedback on this article, as the authors are keen to hear our perspectives.



COVID-19 real-world data

ICH regulators emphasised the importance of international collaboration on observational studies of real-world data in facilitating regulatory decision-making on vaccines and treatments for COVID-19. The January 25, 2021, workshop convened under the International Coalition of Medicines Regulatory Authorities (ICMRA) (<http://www.icmra.info/drupal/en/home>) and co-chaired by Health Canada and the EMA, allowed participants to share information on ongoing initiatives on observational studies derived from real-world data. Key learnings from these activities and opportunities for international collaboration were identified. Regulators also discussed international cohort building; pregnancy studies; and vaccine surveillance and vigilance (<https://www.ema.europa.eu/en/news/ema-preparing-guidance-tackle-covid-19-variants>)

As COVID-19 vaccines are being authorised and rolled out across the world, regulators must ensure the continuous monitoring of their safety and effectiveness, especially when used by special populations. Real-world evidence from observational research is critical to understanding the benefits and risks of medicines in everyday use for the prevention and treatment of COVID-19. The main findings are summarised in this ICMRA report (published February 8, 2021) (<http://www.icmra.info/drupal/covid-19/25january2021>). It is also heartening that non-ICH Regulators have been contributing to the EMA's COVID-19 Pandemic Task Force since December 2020 (https://www.ema.europa.eu/en/documents/other/questions-answers-pilot-project-open_en.pdf) and support these assessments.



EMA Clinical Trials Information System news

Due to technical difficulties, EMA has postponed the launch of the Clinical Trials Information System (CTIS) to January 31, 2022. Full details are on the CTIS page (<https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trial-regulation>). This EMA webpage is dedicated to the CTIS training programme (<https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trial-regulation/clinical-trials-information-system-ctis-training-programme>). Most training is online, but there are a few virtual training sessions in classroom format aimed at Sponsors. Full functionality of CTIS is linked to full application of the European Clinical Trials Regulation EU No 536/2014 (https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf). There will be an 8-year gap between the CTR being adopted and entered into force (2014) and it being fully applicable (2022 – as currently planned), plus a pandemic and the associated innovations in clinical trial design, conduct, reporting, and authorisation that have taken place in between. Outcomes will be interesting to follow.



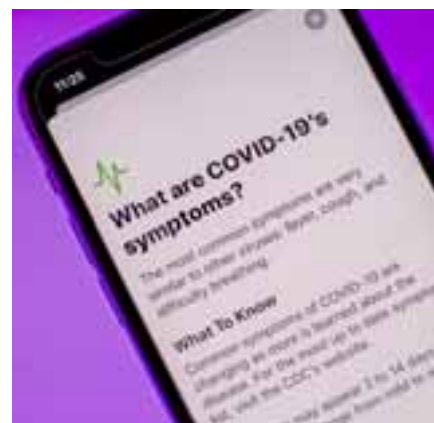
Good Lay Summary Practice update

When the EU's Clinical Trial Regulation (CTR) comes into force, it will require the preparation of a summary of trial results in lay language in addition to a technical summary. Whilst the EU has produced guidelines on the content of lay summaries (https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2017_01_26_summaries_of_ct_results_for_laypersons.pdf), questions remain around their collaborative planning, preparation, and dissemination. The European Forum for Good Clinical Practice and the European Federation of Pharmaceutical Industries and Associations have collaborated in leading a Roadmap Initiative for Good Lay Summary Practice with input from over 60 international patient organisations, pharmaceutical companies, academia, not-for-profit organisations, and clinical research organisations. A public consultation on the recommendations was held in 2020 and further revisions are being considered. The Good Lay Summary Practice recommendations will provide a wealth of useful detail including considerations in planning and design of lay summaries, guidance on writing paediatric lay summaries, and the tricky issue of translation, together with links to glossaries of lay terminology.



Resources

1. "The Impacts of COVID-19 on Clinical Trial Transparency and Document Disclosure PHUSE CTT Project" (https://phuse.global/Communications/PHUSE_Blog/the-impacts-of-covid-19-on-clinical-trial-transparency-and-document-disclosure-phuse-ctt-project) is a December 2020 update (https://phuse.global/Communications/PHUSE_Blog/phuse-covid-19-impact-on-ctt-update) that explains some of the initiatives that have changed since the initial PHUSE Clinical Trial Transparency project launched.
2. EMA's Medical Terms Simplifier (https://www.ema.europa.eu/en/documents/other/ema-medical-terms-simplifier_en.pdf) – a plain-language description of medical terms related to medicines use – is a boon for medical writers preparing patient-facing texts, including the PLS and Patient Information Sheet/Informed Consent Form (PIS/ICF). The resource is housed on the patient pages of the EMA website (<https://www.ema.europa.eu/en/about-us/about-website/glossary>).



Keep yourself – and others – informed

Sign up for emails from the CORE Reference website here: <https://www.core-reference.org/subscribe> to receive "real time" emails about transparency and disclosure impacting regulatory medical writing.

You can review the same information as monthly summaries at:

- <https://www.core-reference.org/news-summaries/>
- <https://www.emwa.org/sigs/regulatory-public-disclosure-sig>
- View it in the monthly EMWA NewsBlast.

If you have news for this RPD Section or any of the aforementioned resources please get in touch and I will gladly share.

EMA's Medical Terms Simplifier is a boon for medical writers preparing patient-facing texts.



This is called the hash, pound, or number character. A hashtag is a keyword or set of keywords that is preceded by the # character. It is used in social media to create a thread of conversations around a specific theme or topic conveyed in short texts or microblogs. It is commonly used in Twitter, Instagram, YouTube, Pinterest, etc.

A dictionary of most common hashtags can be found at <https://www.hashtags.org/definition/~h/>. For your info, EMWA is compiling a list of standardised hashtags for our social media use.



This is called the "at" sign or symbol. The @ sign is part of email addresses and social media user names ("handles"). Our EMWA handles are as follows: @OfficialLEMWA (Twitter), @EMWA (LinkedIn), and @europeanmedicalwritersassociation (Facebook)

The two most important keys on your keyboard

Secondary use of data

unleashing data assets to create value

Janice Branson
Novartis

Mimmi Sundler
Astra Zeneca

Katherine Tucker
Roche

This article was first published in *SPIN*, the quarterly newsletter for members of PSI, an organisation dedicated to promoting the use of statistics within the healthcare industry for the benefit of patients.

Introduction

Over the last decade, there has been increasing recognition in the value of secondary use of clinical trial data. The data may in fact be valuable for other scientific investigations beyond the initial purposes and objectives of the protocol. Across the pharma industry and academia, huge

amounts of clinical trial data have accumulated over many years. Within pharma companies as we plan new programmes and investigate emerging and evolving scientific areas, we seek to understand how we can utilise this already collected data. In 2020 with the urgency of a pandemic situation, we also saw a huge interest in collaboration and intentions to share data across companies and academia. What can we learn from the pandemic experience and how can some of these ideas be incorporated into drug development in order to make drug development cycles shorter and more cost effective? Figure 1 highlights some of the key milestones in the evolution of data sharing and access that we have experienced since 2008.

There are four main areas to consider as we embark on re-use of data: ethical considerations, legal and data privacy considerations, good data science practice, and business sensitivity. In terms of ethical considerations, it is important to utilise

personal data in line with patients' original expectations e.g., aligned with secondary use language in the informed consent form. However, the best practice for secondary data use may be to utilise anonymised or synthetic data where possible. Data privacy elements are covered in more detail below. In terms of good data science,

how do we ensure reproducible research and avoid the reproducibility crisis – can we always ensure analyses plans, data and results follow FAIR (Findable, Accessible, Interoperable and Reproducible) principles? Finally in terms of business sensitivity, re-use of data should be from locked studies only (or those having reached primary endpoint). Depending on the stage

of the programme development lifecycle, the project team should be made aware or involved and any commercially confidential information needs to be accounted for. In addition, if the re-use of data is for the actual organisation that generated the data in the first place, then some of

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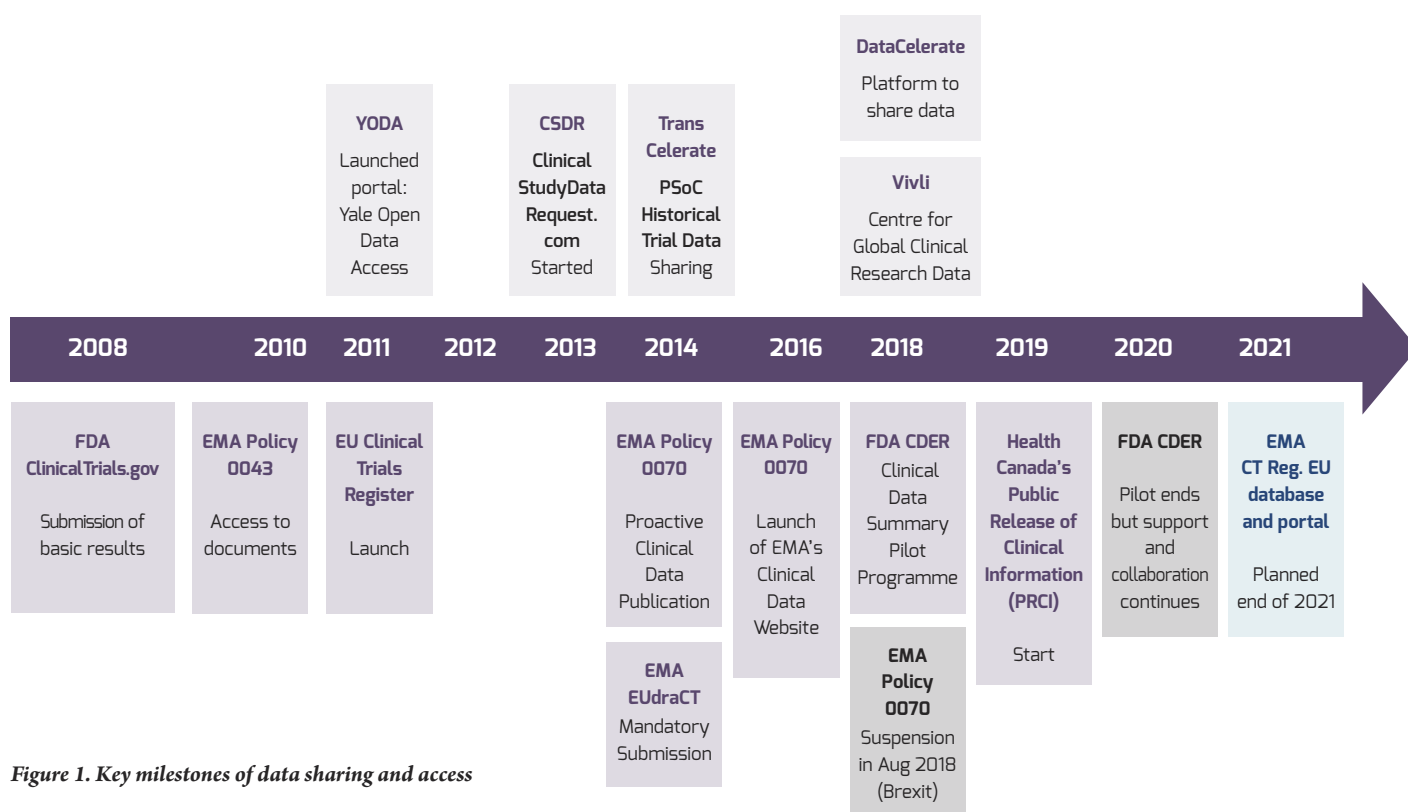


Figure 1. Key milestones of data sharing and access



these considerations may differ slightly compared to external re-use of data. It is true that the external re-use of data has been triggered by public and regulatory pressure on transparency, but there is a growing realisation that internal re-use of data and the considerations that need to be taken into account are still relatively immature within the industry.

Secondary data re-use programmes internally in an organisation

Many larger pharmaceutical companies have multi-year internal data re-use programmes, such as Novartis “data42”, Roche “Enhanced Data and Insights Sharing” and AstraZeneca internal Data Access Policy (iDAP). The aims of such programmes are to bring early and “frictionless” access to R&D data across the broader organisation, including making data “FAIR” (Findable Accessible Interoperable Reusable).

Clinical trial data has value beyond the initial purposes and objectives of the protocol. Data can be used to inform understanding of patient populations and disease, validate new targets, develop new methodologies, endpoints, biomarkers, tools, and other scientific research thus helping develop more “personalised healthcare”, and ultimately deliver greater benefits to patients.

Data re-use programmes should be underpinned with a comprehensive data governance strategy. Such a strategy ensures responsible data re-use in order to maximise scientific insights, at the same time as minimising risks, for example those related to data privacy. Responsible re-use could advance science in the interest of patient

care, ensure data are used maximally for the public good, bring benefits to society, and increase trust in organisations and ethics.

Examples of data re-use objectives include – new insights to characterise the drivers of response to cancer immunotherapy; better understanding the properties of assessment scales used in autism studies (resulting in a change of approach for new studies); enabling clinical and biomarker related questions in a broad breast cancer population, including relationship between certain gene expressions and disease prognosis, thereby informing better designed future studies; identifying groups of super or non-responders.

Data privacy laws and clinical trials

So how do data privacy laws impact our ability to re-use data to answer new scientific questions? “Data privacy” (US) or “data protection” laws (EU) cover the fair and proper use of data about people (“personal data” under the EU general Data Protection Regulation or GDPR). Numerous other countries have their own laws, which may diverge from one another and today there are 100+ country specific data privacy laws. So for a late-stage clinical trial conducted in countries across the globe, this can make a clear assessment of privacy guardrails very challenging.

A pragmatic approach would be to focus on the GDPR as a good starting point. This is true,

even with Brexit since the EU currently recognises the “adequacy” of UK privacy laws, which align with GDPR, at least in the short-term. Under GDPR, clinical trial data is considered as “personal data” and “pseudonymised” (i.e., labelled with a pseudonym). All processing of personal data under GDPR comes with a whole host of obligations on the company, institution or other body including a “legal basis”. In 2019, the EDPB (European Data Protection Board) issued guidance to clarify this for the clinical trials context. It split activities into “primary use” (and further into “reliability and safety purposes” and “research activities”) and “secondary use”. Options for secondary use included analyses deemed “compatible” to the original trial objective, for scientific research purposes and anonymising data.

Data anonymisation

A challenge of anonymisation in the context of global clinical trials are varying data privacy laws and definitions across different jurisdictions. There is no single definition of anonymisation or de-identification (or even terminology). Once data are anonymised, they fall out of the scope of the GDPR (i.e., they are no longer personal data).

However, whilst the GDPR does provide a brief definition of anonymisation (“with all means reasonably likely to be used, data subjects are no longer identifiable”), in practice it is challenging to interpret what this actually means. The GDPR definition lends itself to a more “context-driven” approach. That is, considering the overall context and risks of the data sharing scenario as well as the identifiers present within the data.

However, there are now numerous pragmatic frameworks and materials available to work through anonymisation approaches, some developed by industry organisations such as EFSPi/ PSI, PHUSE, TransCelerate, guidance as part of more formal routes such as EMA policy 0070, Health Canada PRCI (Public Release of Clinical Information) and publications such as the recently updated UKAN ADF (UK Anonymisation Network – Anonymisation Decision-making Framework) and those by Prof. Khaled El Emam. For example, the EFSPi/PSI Data Transparency Special Interest Group (SIG) aims to publish this year on “Anonymising Clinical Data for Secondary Use” and both TransCelerate and PHUSE are working on common definitions

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including anonymisation. There is also hope that the EFPIA GDPR Code of Conduct on Scientific Research will provide some harmonised industry definition when published later in 2021.

Aside from a choice between personal or anonymised data, a third option to consider is generation of synthetic data. Synthetic data are initially generated from actual personal data but ultimately they do not relate to individuals. However, they retain the same statistical properties of the original data, making them a valuable low-privacy risk alternative for certain secondary use purposes.

Putting it all together: Balancing the demands in an evolving landscape

We have covered the bigger picture of data sharing in the pharma industry as some examples of internal data re-use programmes. We also focused on considerations related to data privacy and anonymisation of data. Aside from these, there are numerous other considerations to take into account when building an internal re-use strategy. Ideally, it should be framed within a comprehensive data and information governance strategy and related policies. Some considerations are outlined in Box 1. For example, it is important to consider the flow of data across the entire lifecycle of a clinical trial and when and how in that lifecycle can data be made more broadly available for secondary use (beyond the original objectives of the trial). Development of such a strategy needs to take a truly cross-functional approach to enable detailed evaluation of opportunities and risks.

What can statisticians do to contribute to this discussion? Statisticians are strongly positioned to take a lead in these discussions, both in identifying where secondary use of data may be beneficial within drug development programmes and in ensuring data is collected in a way that will facilitate future data sharing. Statisticians have a deep understanding of the context, trial design and risks associated with a particular trial or molecule and knowledge of the nuances of the data itself. All of these elements are important to inform when data can be made available for secondary use and also in providing this knowledge in the form of associated metadata for the downstream data user.

To conclude, we have seen that external data sharing and collaboration involving the pharmaceutical industry has seen a huge increase in the last 6–7 years via platforms such as CSDR (ClinicalStudyDataRequest.com) /Vivli, TransCelerate, and others. The COVID-19 pandemic saw a massive influx in discussions

Box 1: Considerations when developing an internal data re-use strategy

Use original (personal) data

- The purpose of the re-use is a key consideration
- Definitions – primary and secondary use, wider regulatory activities, compatible use, scientific research
- Role of ICF and its language regarding data re-use
- GDPR legal basis for data processing
- Ability to respond to Subject Access Request
- Dealing with patient consent withdrawals
- How to match planned re-use purpose vs. original protocol objectives and ICF language
- Decision-making

Use anonymised/synthetic data

- How to define anonymisation in an internal context
- Definition of acceptable risk threshold
- Automation via application of standard rulesets to data
- Balancing privacy vs. utility
- How to define “TOMs” (technical and organisational measures)
- Complexity across modalities, ‘linkability’
- Limits on what anon data can be used for (scientific research)
- Processes and assumptions for generation of synthetic data

Other considerations as part of a data governance strategy

- Develop “secondary use” data privacy strategy – philosophy, principles, definitions, ethical considerations, flow diagram, decision-making etc.
- Making data “FAIR”
- Dealing with global studies with patients across multiple countries, implications of different privacy laws
- Defining good data science practices – planning and reporting, reproducibility etc.
- Defining appropriate internal data access rules
- Data flow across study lifecycle, privacy by design
- Systems, processes, infrastructure
- Aspects such as reporting/regulatory status e.g., business sensitivity, use of data pre-database lock; safety signal reporting; restrictions due to co-developments, divestments etc.
- Other laws and regulations e.g., cybersecurity, use of samples, country specific laws, e.g., China “HGRAC”
- Data citizenship and culture, codes of conduct
- Staff awareness, training, knowledge
- Adapting to changes to external guidance

Abbreviations: FAIR, Findable, Accessible, Interoperable, and Reproducible; GDPR, General Data Protection Regulation; ICF, International Classification of Functioning, Disability and Health; HGRAC, Human Genetic Resources Administration of China

across industry on expedited data sharing and dedicated platforms such as Covid19 Data Platform as well as organisations like Vivli and TransCelerate committed platforms to facilitate this. We can learn a lot from the pandemic situation and see how the open and collaborative approach can be applied more generally. It is fair to say many companies have been turning their attention to data as a valuable asset within their own companies and developing internal secondary use policies and programmes. Such a strategy requires a broad cross-functional approach with numerous “dimensions” to be

considered and stakeholders to be included. Such programmes are complex and will develop over many years. Companies need to start thinking about such topics sooner rather than later.

The PSI/EFSPi SIG for Data Transparency considers many of the topics covered in this article: external and internal data sharing and re-use, data anonymisation/data privacy in the context of clinical trial data use. If you are interested in finding out more and contributing to the SIG, *please visit the PSI Data Transparency SIG website*, also for some links to the references in this article.