Roche's Position on Access to & Use of Real World Data

Background and Purpose

In the context of healthcare, real world data (RWD) denotes data relating to patient health which is collected as part of *routine* healthcare practice instead of data generated through conventional clinical trials in dedicated research settings. RWD are seen as a potentially rich and *underutilized source* to generate insight as to how approved diagnostics systems and medicines affect outcomes for patients under real world conditions (for readers not very familiar with the topic it is highly recommended to read *Appendix 2* first).

The purpose of this position paper is twofold: (a) to describe *why* the access to and use of Real World Data (RWD) is—among other stakeholders—of interest to Roche, and (b) to describe *how* Roche addresses various related concerns and intends to foster access to and use of RWD for an overall improvement of the healthcare system.

Roche's Position

…on RWD Relevance and Interest

Roche views RWD as a credible source of scientific information and evidence, provided that (a) the *data is of high, fit-for-purpose quality*, and (b) the *analysis is subjected to scientifically rigorous study design and analytical methodologies*.

The level of data attributes (e.g. in terms of being clinically relevant, accurate[1], complete, transparent, scalable and having longitudinal follow-up) required for such high, fit-for-purpose quality may vary depending on the setting in which the RWD is used, e.g. in exploratory research, development, regulatory decisions, clinical support systems, outcomes-based pricing, reimbursement or other use.

More specifically, Roche believes that the following purposes legitimate the processing and use of RWD, provided that appropriate safeguards are in place:

- protecting the vital interests of patients from prevention through to treatment
- ensuring high standards of quality and safety in healthcare
- addressing the public's interest in an efficient and sustainable healthcare system
- accelerating access to healthcare products and services
- improving personalized patient care
- enabling more efficient scientific and clinical research

Carefully translating RWD into actionable information is an obligation for society as a whole. Arguably, *not* using personal health data could be deemed a risk to the individuals, health systems and societies. Roche is committed to play its role to advance this field, applying the

[1] i.e. it has undergone curation and quality-assurance processes

highest standards and acknowledging that the outcome also may not be favorable for its products.

…on Balancing Individual and Societal Interests

In considering how to regulate the use of RWD Roche believes that policy makers need to strike a balance between (a) the *extent of an individual's control* over his or her individually identified RWD, and (b) other *stakeholders' freedom-to-operate* needed to realize the benefits of de-identified RWD for society as a whole:

Ad (a): Roche concurs with the emerging view that an individual's right to exert control over his or her personal health data *fully extends to the rights under the respective privacy laws, but not beyond that* (unless such rights are voluntarily expanded by explicit mutual agreements). More specifically, Roche maintains that the individual's right to privacy has been fully respected once the individual's data has been properly de-identified (i.e. anonymized or pseudonymized; see *Appendix 1*) according to legal requirements and state-of-the art practices. In contrast, a system, in which an individual's reach would extend beyond de-identification and which would force multiple parties to untangle and extract an individual's data from highly processed data sets at his/her request, is neither practical nor realistic and would unnecessarily stifle scientific, clinical and health economic research[2,3]. In other words, de-identified health data should not be afforded a special status but should be treated with the same level of care and respect as with other de-identified personal data available for analysis.

Ad (b): The potential relevance and value of RWD is built only through the consecutive, laborious and time-consuming steps of collecting, curating, aggregating, de-identifying, cross-linking, analysing, testing against hypothesis, etc. (one can picture this as an 'RWD value creation chain')—at the same time the complexity, required expertise and significant costs increase as well. Policy makers need to formulate a view on how to orchestrate such an ecosystem of public and/or private actors. Currently, different models are emerging. For example, some jurisdictions assign a public entity with the task of establishing a nationwide, structured, de-identified RWD database (e.g. Finland, UK), which in turn enters into contractual (commercial) arrangements with public or private entities for its utilization in research and healthcare practice. Other jurisdictions (e.g. the US) permit the initial holders of RWD (e.g. hospitals) to enter into such contractual arrangements directly. While international harmonization would be desirable to increase RWD's impact, Roche believes that this will not happen in the short term and, therefore, Roche will adapt its approach according to the local prevailing mechanism.

[2] By way of analogy: it would be considered unreasonable for a citizen to request removal of his/her individual census data from population statistics routinely used in making forecasts on infrastructure needs, social security systems, etc. Therefore, an individual's census data is protected by privacy laws and practices, but the de-identified data can be analyzed comprehensively for societal or commercial benefits.

[3] Facilitating the ethical use of health data for the benefit of society: electronic health records, consent and the duty of easy rescue; Porsdam Mann S, Savulescu J, Sahakian BJ; *Philos Trans A Math Phys Eng Sci.* 2016 Dec 28;374(2083).

…on RWD Access and Protection

For Roche, as a matter of principle, appropriate protection of *any* data relating to an individual is an essential pre-condition. Roche generally builds on the *deep data protection expertise* it has gained over several decades conducting thousands of clinical trials and involving millions of patients across the globe.

With respect specifically to RWD Roche has gained *extensive experience* through: (a) its obligation to maintain a comprehensive pharmacovigilance system [4]; (b) performing additional studies with marketed products[5] and (c) collaborations with key data partners and providers to support R&D and patient care and access.

Under normal circumstances RWD supplied to Roche through public or private institutions has already been de-identified and the company has no way of tracking back to the individual to whom it relates. In situations where identifiable RWD is accessible to, or directly collected by, Roche (e.g. through our partner Flatiron Health which is involved in the earlier stages of the RWD value creation chain[6], or mySugr which specializes in an app-based, all-around care approach for people with diabetes[7]) Roche applies appropriate technical and organizational safeguards to protect the RWD (as is the case for clinical trial data): An information security management system is governing all IT systems; rigid identity management and access control concepts are applied; all relevant Roche staff are trained and advised to respect data privacy principles. For more details on Roche's approach to anonymization, pseudonymization and access control to its RWD data please refer to *Appendix 1*.

…on Sharing and Communicating Insights

Roche believes insights generated from RWD can improve R&D productivity and enable personalized patient care and access. Roche is committed to sharing insights that can advance science and medical practices with the broader communities using the appropriate channel (e.g. peer-reviewed journals) to the extent permitted under the data agreements. In general, Roche will ensure transparency in the communication of insights generated by RWD by including the study design, methodology, generalizability, limitations, sensitivity analyses, and other relevant information, and follow published guidance[8] when applicable. Insights that only support internal decision-making (e.g. design of clinical trials) or market arrangements might not be shared in public domains due to the proprietary nature of such activities.

…on Legal and Regulatory Frameworks

The sheer complexity, diversity and historic development of healthcare systems have led to diverse legal and regulatory frameworks across the globe, pertaining to different aspects of

[4] I.e. to collect and report promptly to authorities potential issues with its marketed products and to conduct PMA (post marketing approval) studies

[5] E.g. to generate additional evidence for the use of a drug in a particular indication, or to provide additional evidence for HTAs (Health Technology Assessments) and payers

[6] For more information about Flatiron Health, Inc, please see https://flatiron.com/

[7] For more information about mySugr please see https://mysugr.com/

[8] E.g. FDA Guidance 'Drug and Device Manufacturer Communications with Payors, Formulary Committees and Similar Entities—Questions and Answers'; 13 June 2018

RWD (e.g. data privacy, access and sharing)[9]. Also, policies and regulations are typically established at the national level[10]. While Roche applauds and supports recent calls by policy makers for regional or global alignment, it believes that such common frameworks will take some time to be realized. In the meantime Roche will work with the relevant authorities.

…on Engagement and Dialogue

As has been pointed out by many observers, the overall success of the RWD promise hinges on a collective effort among trusted partners. Roche strives to *build trust actively* in the healthcare community and the wider public by (a) being transparent and forthcoming about its motives and systematic efforts in RWD (e.g. by sharing best practices and use cases with regulators), and (b) working with various stakeholders to shape the RWD debate and to foster acceptance of RWD for research, regulatory and access decision making.

For example, Roche is involved through industry trade associations (IFPMA, EFPIA, MDIC-NEST [11], MedTech Europe, a.o.) and health policy organizations (e.g. Duke Margolis Center for Health Policy) to drive the broad adoption of high quality and security standards and regulations, underscoring that a pragmatic approach to the use of RWD is essential to allow development of new technologies and products and to foster innovation.

Ongoing Initiatives at Roche

Increasingly, it is recognized that major efforts and investments are required to generate *relevant, high-quality* RWD datasets. By way of illustration, here are some of Roche's initiatives: To complement its own capabilities (e.g. developing the Navify® decision support solution to integrate RWD for tumour boards, or the Floodlight Open app to create a more holistic view of multiple sclerosis.), Roche has acquired (or formed partnerships with) a number of companies with novel approaches to RWD. These include for example Foundation Medicine (specializing in genetic profiling)[12], Flatiron Health (curating electronic medical records and providing high-quality data suitable for regulatory use) and mySugr (offering a patient-centric digital health services platform in diabetes care). Roche is now working to integrate/evolve such know-how for the benefit of patients around the world.

With proven expertise in both pharmaceuticals and diagnostics and strong relationships with key industry partners, Roche will continue to embrace ground-breaking technologies not only to drive the digital transformation, but ultimately to take Personalized Healthcare to the next level.

[9] E.g. Estonia established a new e-health-system with a fully digital patient record; Austria is discussing a new "research organization law" which allows access to electronic health records for research purposes.

[10] E.g. in the US: https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RealWorldEvidence/UCM627769.pdf

[11] International Federation of Pharmaceutical Manufacturers and Associations; European Federation of Pharmaceutical Industries and Associations; Medical Device Innovation Consortium, National Evaluation System for Health Technology

[12] For more information please see https://www.foundationmedicine.com/

To reflect the evolving landscape of the RWD topic this position paper will be updated from time to time as needed.

This position paper was proposed by the Corporate Sustainability Committee and adopted by the Corporate Executive Committee on 17 January 2019 and entered into force the same day.

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Encl: Appendices 1-2

Appendix 1

Roche's position on select data protection topics

Basic principles

The right to privacy is a fundamental human right. That is why the protection and responsible use of personal data is anchored in the Roche Group Code of Conduct and reflected in its daily operations.

Roche is committed to collecting and using data in a lawful, fair and legitimate way, and it will always respect the privacy of individuals in order to earn and deserve their trust.

Roche complies with all applicable data privacy laws including but not limited to the Swiss Data Protection Act, the European Union General Data Protection Regulation (GDPR), the US Health Insurance Portability and Accountability Act (HIPAA) and China's Cybersecurity Law and associated data privacy standard.

Anonymization

Data is considered *anonymized* under the EU's GDPR[13], if the data does not identify an individual and there are no reasonably likely means to re-identify the individual. There is a strong demand for a consistent framework and technical standards to overcome the dozens of opinions and concepts that are currently used. For example, in contrast to the EU approach, HIPAA[14] in the US uses the concept of de-identification and has two established mechanisms through which this can be achieved, either by removal of 18 data types which are identifiers or by an expert determination.

Roche keeps RWD identifiable only as long as necessary and RWD is anonymized or aggregated at the earliest possible point in time.

Pseudonymization

Data is considered *pseudonymized,* if the reference to a person is key-coded. Although the data is not directly identifiable, the measures applied are reversible. Without the key—which is always kept separate and secure—one cannot directly identify an individual from such coded data.

In most cases, Roche neither wants nor actually has access to such keys, making it reasonably impossible for it to identify the individuals whose data is in its systems in which case such strongly pseudonymized data may be deemed anonymized, in particular if access to the key is protected by professional secrecy obligations like doctor-patient confidentiality or if the key is entrusted to an independent entity (e.g. a dedicated, public body).

Access to RWD at Roche

Access by *internal* (Roche) staff to systems containing sensitive data such as RWD is controlled and granted to users only according to a need-to-know/need-to-work principle. Prior to sharing any RWD, risk-based assessments are performed to ensure that sharing does

[13] Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation).

[14] Refers to the Health Insurance Portability and Accountability Act of 1996 and its subsequent amendments, 45 C.F.R. §§ 160, 162, 164.

not cause any risks to patients. Recipients of RWD, which are almost exclusively de-identified must commit to avoid undertakings which may lead to re-identification of individuals.

Collaboration with Healthcare Agencies

Roche is actively collaborating with Healthcare Agencies (e.g. European Medicines Agency) on improving patient privacy (e.g. EMA Policy 070).

Appendix 2

Introduction to RWD Considerations

Background

In the context of healthcare, real world data (RWD) denotes data relating to patient health which is collected as part of *routine* healthcare practice as opposed to data generated through conventional clinical trials in dedicated research settings[15]. Such RWD includes—in a narrower sense—data recorded by healthcare professionals in medical health records (e.g. in primary physician offices, specialist offices or hospitals), disease registries, healthcare insurance claims, etc. and—in a broader definition—is often understood to include individual-generated health data (e.g. from wearable devices, patients' own observations, health apps). Thus, RWD may cover a wide variety of aspects such as basic demographic data (e.g. age, gender, domicile), disease/condition-related data (e.g. diagnoses, disease severity, genetic characteristics), treatment history (e.g. surgical intervention, radiation treatment, oral therapy) and even behavior/lifestyle (e.g. physical activity, nutritional regimen). In oncology, it is estimated that RWD accounts for at least 96% of the total pool of clinical data, whereas clinical trials represent the remaining four percent[16].

While clinical trials focus on ensuring that valid causal conclusions can be drawn between intervention and effect, RWD are seen as a potentially rich and *underutilized source* to generate insight as to how approved diagnostics systems and medicines affect outcomes for patients under real world conditions.

In recent years there has been growing excitement in the healthcare community about RWD triggered by four developments:

a) *Increasing availability and quality of RWD in electronic form*: The adoption of digital recording[17], curation capability and storing technologies is making RWD more readily available for curation, analysis and interpretation

b) *Emergence of tools for advanced analysis of large data volumes*: Advances in computing power, data handling and sophisticated analysis techniques are being adapted for the field of healthcare

c) *Increasing limitations of the clinical trial approach*: The classic prospective, randomized clinical trial has its limitations in terms of feasibility[18], time and costs, especially when applied to diseases with long-term outcomes or small patient populations. More generally speaking, it has been stated that progress in science is outrunning the ability of using traditional clinical trials to generate the knowledge required to efficiently translate science into next-generation

[15] Typically, a *clinical trial* means a (relatively homogeneous) group of patients enrolling actively in a randomized study based on pre-planned, authorized protocols to answer specific clinical development questions (e.g. verifying the efficacy of a newly developed medicine).

[16] Based on an estimate that about 4% of all patients participate in a clinical trial, mostly only for a short period

[17] E.g. wearable sensors

[18] E.g. clinical trial population not reflecting 'real world' population; insufficient trial size to detect rare treatments effects; short duration of trial not answering question of optimal dosing regimen or outcome in diverse subpopulations

treatments, regulate drugs or to make informed reimbursement and treatment decisions[19].

d) *Increasing appreciation of the potential value of RWD for patient health and the healthcare system*: There are an increasing number of published, robust examples addressing the need to understand treatment safety, effectiveness and economic efficiency in the real-world settings in various populations and in a real-life environment.

Stakeholders' Potential Benefits

Increasingly, harnessing the full potential of RWD is viewed as a powerful avenue with which—perhaps uncharacteristically—*all* stakeholders in the healthcare system stand to gain:

Patients/Healthcare Providers

Over the last 20-30 years a better understanding of disease heterogeneity (how the impact of a disease can vary between affected individuals), underlying biological mechanisms (the way the disease works in a patient) and new therapeutic modalities (how to get the medicine have its effect in the patient) have enabled interventions to be increasingly targeted to ever more specific patient groups. Now the *addition* of insights derived from RWD offers the prospect of a next level of *Personalized Healthcare (PHC)*, where diagnosis and treatment are highly tailored (and adapted over time) to the individual, both in terms of effectiveness and safety, taking into account the person's unique condition. Physicians and patients are enabled to make faster and more confident decisions, particularly in complex cases, as clinical and patient decision support solutions and their underlying (predictive) algorithms are trained on clinical trial data and RWD.

In addition, the close monitoring and rapid analysis of RWD, may offer patients and healthcare providers the possibility to make new treatment options available more readily (see below).

Payors/HTA Organisations

Once a new treatment is approved, its costs and (health-economic) value are assessed for the purpose of determining (potential) reimbursement. In various healthcare systems this is a mandatory, formal process (HTA, Health Technology Assessment) performed by independent HTA organisations. Here RWD helps to assess the cost-effectiveness of a new therapy which could not be determined from clinical trials alone. Analysis of RWD can gauge the extent to which healthcare providers follow standard-of-care treatment guidelines and evaluate which intervention provides the most promising outcome and has the highest value for the patient.

Similarly, RWD is at the heart of "value-based health care", where "outcomes that matter to patients" and costs of delivering care are measured across the patient journey to ensure that care is delivered in ways that reward value for the patient and by doing so enhances patient and societal value. As a result, RWD opens the prospect of differentiated, dynamic and more

[19] Data rich, information poor; can we use electronic health records to create a learning healthcare system for pharmaceuticals? Hans-Georg Eichler et al., *Clinical Pharmacology & Therapeutics*, September 4, 2018

efficient *outcome-based* payment models instead of *volume-based* models (i.e. 'pay for performance' instead of 'pay per package').

Healthcare Regulators

Given their mandate in public health and their experience in pharmacovigilance, it is not surprising that healthcare regulators recognized the potential of RWD early on. More detailed, readily available information on the effectiveness and safety of diagnostics systems and medicines in the market will greatly improve responsiveness to emerging issues[20].

In addition, RWD can help to accelerate access to important diagnostics and medicines, where clinical trials may prove to be neither feasible nor ethical (see also 'Background' above). For example, in rarer diseases with limited number of patients, the control arm may be supplemented with RWD from patients on standard-of-care treatment ('external control arm'), thereby reducing the number of patients required in the clinical study and, in turn, accelerating its enrollment. This can result in conditional approval, coverage with evidence development and managed entry agreements, where the medicine is approved and funded early under the condition that additional clinical trials or studies within the real-world setting are conducted.

Healthcare Companies

Much of the value from RWD will be realized when a product is entering the market (e.g. by informing regulatory or access decisions for new products). However, RWD may also be instrumental for the development of new diagnostic solutions and medical/non-medical treatment procedures through more efficient clinical trials (i.e. faster site and patient selection), better understanding of unmet medical needs, new insights into disease biology or through identification of potentially new biological targets.

Policy Makers

The more informed use of RWD/healthcare data is expected to bring increased *transparency* into the healthcare system, improve outcomes and make healthcare systems more efficient and sustainable and lead to more effective policy making. (e.g. monitoring of healthcare services, detection of population-level effects, better use of scarce expertise and resource for patient benefit).

The broader notion here is that "everyday healthcare delivery and knowledge generation are intricately linked – not activities separated by an intended or unintended firewall[21]", i.e. the stakeholders are integral parts of a "learning healthcare system" [22].

[20] Real-world evidence and real-world data for evaluating drug safety and effectiveness; J. Corrigan-Curay, L. Sacks, J. Woodcock, *JAMA*, September 4, 2018; vol.320, no. 9

[21] separating "learning" (research) and "using" (everyday practice)

[22] Data rich, information poor; can we use electronic health records to create a learning healthcare system for pharmaceuticals?, Hans-Georg Eichler et al., *Clinical Pharmacology & Therapeutics*, September 4, 2018

Stakeholders' Key Concerns

While the potential of RWD is widely acknowledged, stakeholders have raised concerns which largely revolve around four areas:

Patient Privacy

RWD ultimately originates from individual patients. These individuals generally do not want their medical condition to be known beyond themselves (and their health care providers) and may be concerned about suffering disadvantages or facing discrimination as a result of such disclosure. Patients, therefore, expect that RWD is not abused in any form and that the processing of RWD does not violate their privacy rights. In principle, this can be achieved through *anonymization* of data, i.e. altering or reducing identifiers in a way that it is not possible to identify an individual considering all means reasonably and likely to be used.

However, there may exist tangible and relevant information for an individual patient derived from the RWD analysis which may make it desirable to contact the individual (e.g. to be informed about an undetected and treatable disease). This, however, requires that the removal of identifiers be reversible, which could be achieved through *pseudonymization* of data, i.e. the reference to a person's identity is key-coded and the key is kept by a custodian.

Understandably, patients may be concerned about the robustness of and control over such anonymization and strong pseudonymization approaches (collectively referred to as 'de-identification'[23]), as well as the related data security challenges during collection, transfer, storage and retrieval of RWD.

Data Quality & Interoperability / Scientific Rigour

Unlike the data that are clearly defined, aligned and collected in a clinical trial, RWD comes from a multitude of sources, in a myriad of diverse (non-)standards, and in structured or unstructured formats. As a result of this fragmentation, the quality and reliability of RWD *per se* are a major concern, not to mention the challenge to link/aggregate/integrate such data on a larger scale for useful analysis, or the significant costs associated with resolving these issues (e.g. for curation of data).

In addition, the very nature of RWD means that most studies undertaken with RWD are non-randomized and, hence, may be subject to potential bias/subjective study design and interpretation. As with clinical trials, even the best, quality-assured dataset does not guarantee valid conclusions unless rigorous, state-of-the-art analysis techniques are applied.

Creating and Sharing Insights

Valuable insights may be extracted from RWD with significant efforts by various parties and at various levels as the data is aggregated, processed, linked with other information, tested against scientific hypotheses, etc. Increasingly, the collection and management of RWD have become core activities in the public and private sector. Many stakeholders are seeking

[23] In this paper the term is used in a more common sense; not to be confused with the Health Insurance Portability and Accountability Act of 1996 and its subsequent amendments, 45 C.F.R. §§ 160, 162, 164 (HIPAA); see also Appendix 1.

transparency on the data collection approach, analytical methodologies, roles of different stakeholders, business model associated with the data, as well as how insights are shared[24].

Legal and Regulatory Frameworks

Many aspects around RWD deeply permeate the health care system and society. Besides the privacy and technical aspects outlined above, there are numerous open legal and ethical questions. For example, there are diverging views and practices as to who should have the control/distribution/usage rights over RWD (i.e. who 'owns' the patient data) – the patient, physician, hospital or national health care system? There is also concern that an ever increasing stratification of patient populations (and the transparency thereof) may lead to unwanted social pressure and deteriorating solidarity.

Consistent and transparent frameworks addressing such technical, legal, ethical and governance questions are *essential* to provide clarity, stability and ultimately trust among all stakeholders. While there have been multiple calls for action at the international[25] and national level, much is still (early) work-in-progress.

[24] In this context it is worth noting that these insights frequently will be beneficial only to future patients, not to those who contributed the original data.

[25] e.g. OECD Council Recommendation on Health Data Governance, January 2017; Communication from the EU Commission on 'enabling digital transformation of health and care in the Digital Single Market', 25 April 2018