

**Making Compassionate Use More Useful: Using real-world data, real-world evidence and digital twins to supplement or supplant randomized controlled trials**

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The coronavirus pandemic has placed renewed focus on expanded access (EA) programs to provide compassionate use exceptions to the waves of patients seeking medical care in treating the novel disease. While commendable, justifiable, and compassionate, EA programs are not designed to collect the necessary vital clinical data that can be later used in the New Drug Application process before the U.S. Food and Drug Administration (FDA). In particular, they lack the necessary rigor of properly crafted and controlled randomized controlled trials (RCT) which ensure that each patient closely monitored for side effects and other potential dangers associated with the drug, that the data is documented, stable and are traceable and that the patient population is well defined with the defined target condition. Overall, while RCTs is deemed to be of the most reliable methodologies within evidence-based medicine, morally, however, they are problematic in EA programs. Nevertheless, actionable data ought to be collected from EA patients. To this end, we look to the growing incorporation of real-world data real-world evidence as increasingly useful substitutes for data collected via RCTs, including the ethical, legal and social implications thereof. Finally, we suggest the use of digital twins as an additional method to derive causal inferences from real-world trials involving expanded access patients.

*Keywords:* Real-World Data, Real-World Evidence, Randomized Clinical Trials, Randomized Controlled Trials, FDA, Bioethics, Digital Twin, Machine Learning, GAN

## 1. Introduction

### 1.1 *Compassionate use*

Compassionate use is a catchall lay term<sup>1</sup> for various legal shortcuts in providing access to experimental and limited-access medications.<sup>2</sup> Many jurisdictions worldwide provide for different levels of compassionate use of in-clinical-trial or unapproved pharmaceuticals under varied legal oversight by their respective regulatory bodies.<sup>3</sup> Broadly, these regulatory programs provide limited access exceptions —alternative legal means to access that missed opportunity— particularly for desperate patients who can't otherwise legally obtain a medical product. Most commonly when a patient is unable to join an ongoing clinical trial.

These loopholes have legal limitations. In the United States, for example, there is no constitutional right to compel access to said pharmaceuticals, even for terminally ill patients.<sup>4</sup> It remains up to the various stakeholders in the process, such as the doctors, pharmaceutical companies, institutional review boards and regulators to decide whether to help the patient.<sup>5</sup> In some cases, courts have allowed pharmaceutical companies to terminate access even while patients are still using the drug, arguably effectively.<sup>6</sup>

In the US there are several compassionate use programs including a federal Expanded Access (EA) program that is ultimately administered by the Food and Drug Administration (FDA) for medical products under Investigational New Drug Applications.<sup>7</sup> The EA program is distinct from the similarly sounding and acronymed, but rarely implemented<sup>8</sup> Emergency Use Authorization (EUA) which allows the FDA to facilitate broad access to an unapproved or differently labeled drug during a declared state of emergency, such as a pandemic;<sup>9</sup> in contrast to the 'effectiveness' standard for FDA approval under conventional conditions, EUAs require a much lower 'may be effective' standard to be approved.<sup>10</sup> EUA access to medication circumvents much of the minimal infrastructure of EA access, and so is not part of this analysis.

The FDA's EA program, enacted in 1987,<sup>11</sup> sought to codify a long-standing ad hoc system.<sup>12</sup> Per 21 CFR 312.300 et seq, the FDA was tasked with facilitating "the availability of such drugs to patients with serious diseases or conditions when there is no comparable or satisfactory alternative therapy ..." If preconditions are met, the FDA allows for distribution of the drug even prior to market approval of the drug.<sup>13</sup> These access programs are not necessarily small or limited in size or scope: in some cases, thousands of patients were provided investigational drugs prior to their final FDA approval.<sup>14</sup>

The approval process for EAs can be relatively onerous. It requires a physician to sign on to the project, the acquiescence of the drug company to provide the drug, and the eventual approval of an institutional ethics review board (IRB) and the FDA. The patient must have exhausted all their options before an EA opportunity is even considered. Federal and state laws also provide for even less onerous paths to access investigational drugs through various Right to Try (RTT) regulations.<sup>15</sup> However, in contrast to EAs with their at least tenuous ties to FDA oversight, RTT wholly abandons the FDA's gatekeeper role, requiring no IRB (as per the federal statute, although state statutes vary) or any FDA approval for the requested access, just the approval of the treating physician and the drug manufacturer.

In EAs, given the possible negative outcomes, both the doctor and the drug company are disincentivized to approve a Hail Mary use of an unproven drug for an individual that otherwise did not qualify to be part of a clinical trial. Some manufactures fear both the repercussions to their subsequent new drug application (NDA) as well as bad PR given the

probability of poor patient outcomes. (Historically, the former fear has been unfounded; there have been less than a handful of cases where an EA program had a negative effect on the drug labeling.<sup>16</sup>) As such, only a percentage of requests ever end up at the final step of seeking FDA approval. The FDA approves more than 98% of all requests that reach the threshold, depending on the year, of the around a thousand per year expanded access requests<sup>17</sup>. The FDA has even recently mandated additional efforts to further facilitate access to the EA programs.<sup>18</sup> A website was recently developed to facilitate the process for patients and their advocates.<sup>19</sup>

But even if the EA programs do not have a proximate effect on the NDA or the pharmaceutical company's bottom line, they ultimately take away limited resources and possibly even consume limited drug supply that could have gone to additional patients within a structured clinical trial.<sup>20</sup> Moreover, EA efforts don't produce much useful data for the final drug approval. Thus, while such programs may be immediately helpful for a small number of desperate patients, they are often unhelpful for the much larger group of patients that will benefit from the 75% of EA drugs that are eventually approved by the FDA.<sup>21</sup>

## ***1.2 Compassionate use during the pandemic***

The coronavirus pandemic has placed renewed focus on the FDA's EA programs. While commendable, justifiable, and compassionate, from a utilitarian point of view—which is an underlying philosophy for other FDA regulations as well<sup>22</sup>—EAs are arguably wasted opportunities and wasted resources. EA programs are rarely able to collect the necessary vital clinical data that can be later used in the New Drug Application (NDA) process before the U.S. Food and Drug Administration (FDA). In particular, they lack the necessary rigor of properly crafted and controlled randomized controlled trials (RCT) which ensure that each patient is closely monitored for side effects and other potential dangers associated with the drug, that the data is documented, stable and are traceable and that the patient population is well defined with the defined target condition.

## ***1.3 What is an RCT?***

The FDA considers the RCT to be the best research program for use in generating data for an NDA for a number of reasons, including: (i) RCTs are optimally largely separate from routine clinical practice without its concomitant confusing data. Further, (ii) through the rigorous nature of its development, the RCT is specifically designed to control variability and to maximize data quality. And, in contrast to EA programs, (iii) RCTs have restrictive eligibility to limit participants to certain characteristics and homogeneity such that the detection of an effect of a drug, if any, is more concretely determinable.<sup>23</sup> Although this can also become a problem when an NDA is approved and an untested portion of the population reacts unexpectedly. Also, (iv) there is division between the research and the clinical through particular procedures and protocols, data collection systems and even the use of non-clinical personnel.

It is because of these central characteristics that RCTs—thought to have been around at least since 18<sup>th</sup> century when James Lind conducted controlled experiments relating to scurvy—are the universal gold standard in establishing efficacy and safety data for an entire population, and trusted to answer the important NDA questions: does the drug actually work;

do the benefits of the drug outweigh the risk; and, what is the optimally safe dosage and regimen. Importantly, for FDA labelling, the evidence must be fully supportive of the conclusions. The RCT has long provided that necessary support. Nevertheless, RCTs are evolving. Versions now include hybrid designs that collect less standardized data, as well as pragmatic-styled trials that may more closely reflect clinical rather than research standards.

### ***1.3 EA data and NDAs***

EA data has historically not been seen as particularly relevant to the NDA application.<sup>24</sup> In contrast to RCTs, EA data is currently not seen to be fully supportive of the necessary conclusions: they are not well controlled, patients are less well defined, neither the participants nor the researchers are blinded making it harder to support causal inferences, adherence to regimens are far from assured, and they lack the organizational support of standard RCTs with their monitoring and evaluations.<sup>25</sup> And while there have already been some efforts to include EA data within the regulatory review of therapeutics, the data is often weak.<sup>26</sup>

That ought to change. With an increase in the frequency of requests for EAs, the FDA ought to consider both practical changes in the way data is, if at all, systematically collected from EA programs, and regulatory changes that would allow this new data collection to be better included in an NDA.

One possibility is the development of EA programs designed to effectively collect relevant and even actionable real-world data (RWD) —which can originate from non-standard data sources. Data collected from EA participants, both prospectively and retrospectively could potentially be used as real-world evidence (RWE) that would support efficacy and safety determinations applicable to the FDA drug approval process.

## **2. Real-World Information**

### ***2.1 Real-world data in trials***

The immediacy and urgency of the COVID-19 pandemic has resulted in a growing appreciation for the need to collect more data faster. Even without the need/opportunity to collect data from EA programs, RCTs are inherently tedious to design and implement. The use of RWD to create RWE would provide an additional source of usable data to help push the regulatory decision-making process forward as well as providing valuable post-market data. The growing push to include RWE<sup>27</sup> has been proposed for pharmaceuticals, vaccines and medical devices.<sup>28</sup>

Pharmaceutical RWD falls across a broad spectrum of confidence. The data is rarely robust enough to allow for causal inferences, especially difficult when the treatment effects from the drug are not large in general. But RWD, even in EA situations, do not have to be poor versions of data collected via RCTs. EA-based trials can be designed to create RWD with sufficient confidence levels that they can be included in the new drug application, if not even replace RCTs. Non-RCT trials have already been proposed and used in the NDA process: these include non-interventional clinical observational-type studies, historical retrospective analyses, and pragmatic trials that are more clinical than research in nature.

The incorporation of RWD and RWE is mandated. The 21st Century Cures Act (Cures Act) requires the FDA to set “standards and methodologies for collection and analysis of real-world evidence” while providing broad leeway to find other applicability for this type of data. Section 505F of the Cures Act specifically defines this RWE broadly any “data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than randomized clinical trials.” As per the Cures Act, the FDA is obligated to seek alternatives to the expensive, narrow and rigid RCT paradigm and, among other efforts, incorporate RWE into its approval process. The FDA and other third parties have already developed numerous guidance documents,<sup>29</sup> initiatives and frameworks including apps, to this end.<sup>30</sup>

However, without reassessing how RWD is collected and extracted, and without designing robust EA programs that focus on extracting actionable, reliable and transparent RWE from RWD we are far off from achieving the Act’s goals. Currently there is no unified system that allows evaluation and quality comparison across various RWD sets; we are far from replacing the RCT through RWD extracting trials, although there are efforts.<sup>31</sup>

## ***2.2 Real-world data and real-world evidence***

The FDA, in its guidance documents draws a distinction between RWE and the RWD that support it. In particular, RWE must be evaluated in light of the reliability and relevance of the underlying data. To this end, the FDA defines RWD as “data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources,” and RWE as “the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD.”<sup>32</sup>

RWD can be extracted from numerous sources, including: electronic health records (EHR), although EHRs will typically only collect major events, and not daily relevant data outside of hospitalization,<sup>33</sup> various data associated with the administrative provision of health care, including billing, claims, and insurance data, self-identifying information provided by individuals to patient registries, groups, social media pages and the like, and information collected by professional and recreational internet of things (Iot) devices ranging from insulin pumps to Apple Watches and Fitbits.

RWD fits in well with continually expanding universe of Big Data: Broadly speaking, big data is defined by at least 4 V’s: velocity, variety, volume, and (lack of) veracity. RWD is similarly defined, it can be collected in real, or near-real time, from a host of diverse sources, providing innumerable data points, but due to its sources and structure, lacks the veracity of standard clinical data. Notably, the FDA does not yet see RWE as sufficient to stand on its own, but rather as simply further support and additional data collected through “randomized trials (e.g., large simple trials, pragmatic clinical trials) and observational studies (prospective or retrospective).”

Moreover, the use of RWD may not, as per the FDA, always result in RWE that can be used directly toward a clinical drug trial. Still, the FDA already sees value in RWD in optimizing the trial process itself, even if it cannot be used towards an outcome. For example, in generating new hypothesis to test via RCTs, identifying relevant biomarkers and prognostic indicators, or assessing various inclusion/exclusion criteria.

But these limitations can be overcome. The use of RWD within clinical drug trials themselves, while still limited, is expanding in many different jurisdictions and have even been incorporated into a handful of NDA submissions. To its credit, the UK, under the Early Access to Medicines Scheme, was the first to allow RWD from a compassionate use program to be officially considered as part of regulatory submission.

The FDA has published numerous recent papers relating to RWD and RWE, signaling their intent to promote their use.<sup>34</sup> The FDA has shown additional interest in this area in the recently published a Funding Opportunity Announcement that seeks to examine a number of potential applications of RWD in the drug regulatory process.<sup>35</sup> Even more recently, the FDA further announced its participation in the COVID-19 Diagnostics Evidence Accelerator organized by the Reagan-Udall Foundation.

## ***2.2 Real-world limitations***

The RWE and RWD FDA frameworks are intended, as per the Cures Act to be developed in consultation with stakeholders. Outside of their incorporation into EA-based clinical trials, RWD and RWE are thought to also be useful expanding clinical trials into more rare diseases<sup>36</sup> and cancers<sup>37-39</sup> where RCTs are harder to develop, developing tools to estimate the effectiveness of treatments, increasing the diversity of the clinical trials in general, expanding the usability of the results into new interventions and comparisons of alternative interventions, creating actionable data where RCT opportunities are limited, adding evidence from broader studies, learning more about safety concerns in the broader population, doing more comprehensive risk/benefit analyses beyond simply efficacy, and appreciating how the drug actually acts under less constrained conditions than the ones provided in an RCT.

To accomplish this, major limitations associated with RWE and RWD need to be attended to, especially lack of structure and standardization, biases, and confounding factors, and concerns with clarity and the relevant clinical granularity from the sources. This is non-trivial: Biases and confounding factors are typically dealt with through randomization, eligibility criteria and follow-up audits, which are much harder to accomplish with RWD.

These biases include, information biases stemming from errors in data capture, lack of standardization, or incomplete data retrieval due to holes in the data, limited access to the relevant data; attrition biases resulting from patients that wholly drop out of any structured surveillance, compliance or performance bias, given the unstructured nature of RWD collection, patients might not be as incentivized to adhere as effectively to treatment; confounding biases as a result of the heterogeneity of the patients, including but not limited to patient demographics, their environment, their health environment including their provider and clinical settings, the use of alternative therapies, and the patients' comorbidities; immortal time biases when we cannot ascertain when patients began being tracked, and selection bias of the patients and the choice of therapies made by their physicians, among many other potential biases. RWD also creates, at least in the outset, additional costs especially relating to sourcing, capturing, standardizing, cleaning, integrating, analyzing via data science tools, bioinformatics, natural language processing and machine learning the data, and even encrypting the data such that patient privacy is protected.

Patient privacy is another non-trivial concern. RWE requires the collection of a wide variety of hard to anonymize datasets such as insurance records, social media information and electronic health records. Anonymization of this data can raise costs and hinder its utility. And re-identification from correlating data with other public databases is always a possibility creating additional regulatory hurdles: The European General Data Protection Regulation (GDPR) is particularly onerous here.

### 3.0 Making RWD Work

But for all of its limitations and complications RWD may become an invaluable source of data for pre-clinical drug trials and NDAs, especially RWD culled from EA related trials. Desperate times allow for the development and implementation of methods and technologies that heretofore have not found mainstream approval. A number of these technological and regulatory wallflowers have recently found greater traction, including distance learning, telemedicine, universal basic income,<sup>40</sup> and potentially now RWE and RWD.

RWD is a technology that has been waiting for an opportunity to spread its metaphorical wings. More than just providing more of the same, RWD is potentially less demographically homogenous than standard RCTs which often underrepresent minorities and often do not represent a spectrum of clinical presentations, and can miss additional useful datapoints that might not be collected within the rigid structure of the RCT. RCTs are expensive, unwieldy and often difficult to implement especially in low-incidence diseases.

Now is the opportunity for the FDA to set standards for data collection related to EA programs with a focus on reducing design flaws and biases. Under EA programs, the FDA can incorporate requirements on both the patient, the managing physician and the pharmaceutical company to follow guidelines to limit the number of incomplete data sets and variabilities in data collection.

Additionally, data should be collected and curated such that it is meaningful and actionable. Standards such as ICD-10<sup>41</sup> and HCPCS<sup>42</sup> should be employed when applicable, and data should be expedited such that it can be collected and shared in real-time, and transparent in that it can be reproduced and replicated, in addition to being verifiable by auditors.<sup>43</sup> This last is especially important as outside of the controlled environment of clinical studies, there is a concern that physicians and/or patients will consciously or subconsciously cherry-pick data to report.

One of the greatest limitations of RWE relates to the difficulty in making causal inferences from the data, especially when there is no placebo data to counterbalance the collected data. The incorporation of placebos are especially ethically problematic when the RWE comes from compassionate use programs.

#### 3.1 Digital twins

One way to circumvent this particular limitation is through the use of digital twins, i.e., the development of in silico representations of real-world objects. In silico digital twins began being developed in earnest around the turn of the century, originally conceived for NASA space vehicle product lifecycle management<sup>44</sup> they have been heretofore used

primarily in engineering fields wherein devices can be stress-tested without building a second device.<sup>45</sup>

The engineering concept was designed such that the virtual and physical systems would be linked throughout the entirety of the product lifecycle, from creation, through production and operation and eventually disposal.<sup>46</sup> Nevertheless, digital twins don't have to necessarily be linked and mirror the physical device exactly. They can also be predictive wherein a range of potential future states can be created and tested independently on the digital twin.

This ability to run computer simulations on virtual objects allows devices to be tested even before they are fully built and/or deployed. Digital twins range from small devices to even cities, with varying degrees of complexity. The virtual system is designed to mirror, as closely as possible all the complexities of the original system.

Digital twins are non-trivial to design and they require complicated modeling, advanced computing power and huge amounts of data to accurately reflect the physical object. The complexities are further exacerbated when creating a digital twin of a living organism that also exists and operates in a complex dynamic living environment. Nevertheless, published patent applications<sup>47</sup> and some early papers<sup>48</sup> suggest that there are significant efforts in the early development of patient digital twins.

One promising example are simulator engines being developed by Unlearn.AI with the goal of simulating patient populations, disease progressions, and/or predicted responses to various medical treatments.<sup>49</sup> The company uses an unsupervised machine learning model called a Conditional Restricted Boltzmann Machine (CRBM) to simulate detailed patient trajectories.<sup>50</sup> These digital twins are intended specifically for the treatment of neurodegenerative diseases, including, Alzheimer's Disease and Multiple Sclerosis. Termed digital subjects by Unlearn.AI, they provide "... a computationally generated clinical trajectory with the same statistical properties as clinical trajectories from actual patients. ... they present no risk of revealing private health information and make it possible to quickly simulate patient cohorts of any size and characteristic."<sup>51</sup> Others have developed synthetic individuals from real-life data to predict aging and mortality trajectories via tracking predicted health deficits that accumulate through damage.<sup>52</sup>

Succinctly, in the medical context, demographic data, family history and other unstructured health data, electronic health records, laboratory results, physiologic measurements and insurance data, imaging and signal data as well as substantial 'omic data (genome, microbiome, transcriptome, proteome, metabolome and others<sup>53</sup> (e.g., all the stuff that can also be termed RWD) can be collected and used to develop as close as representation to the original patient as possible, for example, via machine learning technologies.<sup>54</sup>

In a number of examples, generative adversarial networks (originally developed by Goodfellow et al<sup>55</sup> and heretofore used primarily in imaging processing to generate synthetic content) have been proposed.<sup>56</sup> In one early study, a GAN was employed to predict clinical outcomes via the determination of the trajectory of laboratory tests, based on data culled from thousands of patients.<sup>57</sup> In another, a GAN was used to create synthetic electronic medical records that closely fit real data.<sup>58</sup>

However, with all their promise, digital twins and similar predictive efforts are still limited by the heterogeneity of data and inability to generalize across widely different datasets ostensibly collecting the same data. Further, the data privacy concerns discussed above also relate to digital twin development, especially as data needs to be collected that not only relates to the physical patient and their *in silico* twin, but also the development of the technology itself will require the collection of data on various non-trial related individuals in optimizing the algorithms.

#### 4.0 Conclusions

The ability to extract casual inferences is fundamental to clinical trials. The validity of these inferences are bolstered by many of the attributes of clinical trials that have become *de facto* in the industry, including: double blind randomized controls via placebos, homogenous sample populations, transparency, standardization and oversight. The recent pandemic has highlighted the limitations of these types of trials, especially when regulatory bodies provide broad expanded access to promising therapies in the second and third stages of their clinical trials.

While our humanity demands that we do our utmost to help patients in need, the provision of unproven trial drugs to patients that cannot be included in the data-creating trials creates numerous practical, legal and ethical problems. Practically, EA programs take potentially scarce resources, such as trial drugs that do not yet have dedicated manufacturing platforms, as well as clinical personnel, away from a clinical trial. This redistribution of scarce resources, often politically motivated, or influenced by the potential for both positive<sup>59</sup> and negative public relations, is aggravated by the current practical and legal inability to parlay the potential information collectable by those receiving compassionate use of the drugs into the dataset of the clinical trial and toward the NDA.

COVID-19 has created increasing demand for EAs and the resulting data applicability to NDAs is unclear at this early stage.<sup>60</sup> In one example, Gilead Sciences was flooded with expanded access requests for an unapproved investigational drug Veklury (remdesivir), which it initially had to halt, due to the overwhelming nature of the demand and its effect on the concurrent clinical trials. Subsequently, with the declaration of a public health emergency, the FDA issued an EUA for remdesivir for hospitalized patients with COVID-19.<sup>61</sup> While the FDA does not have the authority to force a pharmaceutical company to provide the drug,<sup>62</sup> its likely more difficult from a PR standpoint to refuse an EUA.

While the risk benefit calculus for the individual patients often favors granting EUAs<sup>63</sup> as well as EAs. From a utilitarian viewpoint of maximizing social benefit, they can be seen as problematic as they place the immediate and statistically unproven need of the few receiving expanded access medications ahead of the need of a general population that may benefit from the final approved drug. (Notably, COVID-19 has resulted in other wasted resources due to the fast and furious rush to publish in the field.)<sup>64,65</sup> If the EA programs and their associated inability to generate actionable data push off the NDA, then there is the possibility for substantial harm to the broader population, especially when the drug is a promising opportunity to minimize the effects of the pandemic.

But EUA and EA patients need not be deprioritized. There is a regulatory solution: the decision by regulatory agencies to develop usable methods to extract RWD from EA programs that have been heretofore axiomatically unable to approach the rigor of an RCT to create RWE that can be used toward an NDA. There is already a regulatory drive to find opportunities to include RWD and RWE into the NDA process, for example in vaccine development.<sup>66</sup> Clearly, pandemics provide the opportunity for regulatory agencies like the FDA to set up standards and best practices as to how to extract the most useful and actionable data from the heterogenous often mortally-ill patients that access pre-clinical drugs through the various expanded access programs.

Moreover, with the moral problems with providing placebos to expanded access patients, the FDA and other regulatory agencies should pursue the emerging area of biomedical digital twins. Already a maturing technology in areas such as aerospace, digital twins and other in silico biomedical data predicting and data synthesizing technologies can provide opportunities to test placebos on virtual rather than real patients to minimize confounding factors typically associated with RWD and RWE and finally enabling the enhanced derivation of casual inferences from real-world non-clinical data. Such efforts might even promote enhanced internal and external validity,<sup>67</sup> something that we cannot as yet accomplish from RCTs alone.

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