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Making It Count: Extracting Real World Data from Compassionate Use and Expanded Access Programs

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The worldwide Coronavirus pandemic has resulted in a worldwide scientific goldrush aimed at identifying, characterizing, diagnosing, treating and eventually preventing the spread of COVID-19. Researchers everywhere seem to have hastily dropped their own current projects in lieu of the timelier and perhaps more lucrative focus. Unfortunately, this scramble for solutions under extremely extenuating circumstances, can come at the expense of organized responses employing reliable scientific methodologies and comprehensive data collections. Thus, although pandemic science has advanced substantially because of this extraordinary and unprecedented concerted effort, there still may have been a squandering of limited time, money, facilities and data collection opportunities on potentially redundant and overlapping ventures. This is especially problematic in pharmaceutical research where similar drug studies are vying for the same limited groups of patients (London and Kimmelman 2020).

Expanded Access (EA) programs worldwide provide compassionate use exceptions to cohorts of patients who are unable, for a variety of reasons, to join an ongoing pharmaceutical trial and still receive an investigational drug prior to its final approval. Broad application of EA programs can create even more missed scientific opportunities, as participants, drugs, money and data are shunted away from standard clinical trials to less formalized crises-driven EA programs.

The FDA's system of expanded access, enacted in 1987 arguably in response to the AIDS epidemic, sought to codify the long-standing ad hoc system that had allowed investigational drugs to be provided for treatment to seriously ill patients (Zoffer 2019). 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 to diagnose, monitor, or treat the patient's disease or condition." If preconditions are met, then the FDA can allow for even widespread distribution prior to market approval of the drug. (21 CFR 312.320) There have been numerous instances where thousands of patients were provided investigational drugs prior to their final approval (Young et al. 1988).

Notably while the FDA has created a clear regulatory pathway for emergency and compassionate access to investigational drugs, there is no constitutional right to compel access to said pharmaceuticals, even for terminally ill patients (Abigail Alliance v. von Eschenbach 2008). Regulatory bodies cannot force drug manufacturers to provide an often costly and scarce drug, especially at the expense of their parallel clinical trials. Further some manufactures may 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 (Jarow and Moscicki 2017).

The FDA approves more than 98% of the around a thousand per year expanded access requests (Mckee

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et al. 2017) and has even recently instituted additional efforts to further facilitate access to the EA programs (FDA 2019). Similarly, US federal and state laws have provided for even less onerous paths to access investigational drugs through various Right to Try (RTT) regulations. However, in contrast to EA programs with their 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 manufacturer of the drug.

Overall, the RTT pathway is less defined regulatorily, particularly regarding the recoupment of costs, or in the exact nature of the required informed consent. Also, adverse reactions need not be reported to the FDA under the RTT rubric. Prior to its enactment, researchers had questioned the ethics of providing this even more streamlined entrée to not yet proven remedies.

The European Medicines Agency provides nonbinding recommendations to national competent authorities for compassionate use of unauthorized medicines (EC 726/2004, Art 83), but member states each implement their own procedures and rules, under various different designations. Many European jurisdictions similarly provide RTT-like programs which are also designed to circumvent the national regulatory bodies (Balasubramanian et al. 2016).

And like the broader Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 (PAHPRA)'s Emergency Use Authorization (21 USC 360) which facilitates access to unapproved medical countermeasures (MCMs), Israel's Clause 29(c) of the 1986 Pharmacist Regulations similarly provides protocols and procedures for access to medication during pandemics, while also carving out regulatory approval for more personal expanded uses.

Notwithstanding the political attractiveness of the ever-expanding compassionate use programs, around 25% of drugs that are procured through these programs never obtain final FDA marketing approval, indicating the continued value of the FDA as a gatekeeper in withholding access to drugs that ultimately may do more harm than good (Miller et al. 2017).

But safety of the patient is not the only concern when it comes to critiquing expanded access systems. Optimal benefits for the broader society are best achieved when patients are enrolled in properly crafted randomized clinical trials (RCT) which not only ensure that each patient is adequately protected from side effects and other potential dangers associated with the drug, but are the universal gold standard in establishing efficacy and safety data for an entire population.

Thus, we argue that an optimal pragmatic expanded access program would better serve society, even in a pandemic, if it was designed to produce substantial actionable data for inclusion in the eventual NDA. Currently EA data is often not seen as particularly relevant to the NDA application (Chapman et al. 2019). And while there have already been some efforts to include EA data within the regulatory review of therapeutics, more is needed. This requires both practical changes in the way data is, if at all, collected from EA programs, and regulatory advances to allow this new data collection to be better included in an NDA.

Perhaps most useful, EA programs ought to be devised and developed such that real-world data (RWD)—which can originate from electronic health records, medical device internet of things (mdIoT) (Sherman et al. 2019), family history, insurance claims and even social media—can be collected from EA participants and used as real-world evidence (RWE) of efficacy and safety applicable to the FDA drug approval process.

Already, the use of RWD within 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 (PWC 2016).

RWD could even soon be a required component of an NDA. As per the 2016 Twenty-First Century 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 initiatives and frameworks including apps, to this end (Baumfeld Andre et al. 2019). However, trials that focus on extracting RWE from RWD, which still lacks a unified system that allows evaluation and quality comparison across various data, are far from replacing the randomized clinical trial (Bartlett et al. 2019), although there are even efforts to overcome these limitations (Gliklich and Leavy 2019).

Practically, EA programs that collect RWD will for the foreseeable future present numerous concerns with regard to the collection of usable and actionable data vis-à-vis FDA approval of a pharmaceutical,

including the lack of standardization of reporting, biases in the various aspects of the patient recruitment and subsequent data analysis, heterogeneity of research structure, lack of infrastructure and financial wherewithal to collect data on par with standardized trials, the disconcerting health of the patients, lack of reliability and validity of the data, and the introduction of many confounding variables (Klonoff 2020). Some of these concerns can be mitigated through the grouping of patients into useful cohorts, the establishment of patient registries and greater collaboration with the FDA in the structure of EA programs (Reagan-Udall Foundation 2018). But until these concerns are competently dealt with, we are unlikely to see broad acceptance of EA RWD data in an NDA.

One particularly thorny issue is that pragmatic EA trials do not employ the foundational control placebos central to RCTs; it would be ethically abhorrent. One potential solution might be to develop AI digital twins of each patient within the EA cohort based on available health and medical data. AI digital twins, a long-standing feature of engineering studies (Grieves 2019), could potentially replace the need for actual placebo controls to assess what would have happened to the patient had they been given the placebo instead of the investigational drug; rather than putting a real patient at risk, researchers could virtually test the digital representation (Fisher et al. 2019).

In a time characterized by two very different viral pathogens, misinformation and SARS-CoV-2, we need to acknowledge the first to deal with the latter. Hopefully, as things like mdIoT data collection matures and standardizes, RWD becomes more reliable and actionable, and innovative technologies are incorporated into EA data collection, we will be able to further facilitate expanded access to life-saving drugs, without the fear that saving one life could affect the lives of many others that are depending on reliable trial data.

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More than Warm Fuzzy Feelings: The Imperative of Institutional Morale in Hospital Pandemic Responses

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The COVID-19 pandemic has created or exacerbated numerous crises threatening social, economic, and political institutions around the world. While it has received far less attention than the public health and economic fallout from the virus, many clinicians and hospital staff have raised worries about the consequences of the pandemic for morale within healthcare institutions. Some institutions responded admirably in partnership with clinicians and staff but many hastily developed and implemented new policies and procedures with inadequate input from diverse stakeholders and failed to provide transparent and consistent rationales for decisions. Clinicians reported experiencing unprecedented "chaos caused by constantly changing and conflicting guidance," especially pertaining to new policies and procedures around testing, PPE, masking, and visitation (Rosenbaum 2020). However well-intentioned, the management and communication of these policies and procedures undermined the workforce's ability to adjust and increased anxiety about both risk of infection and institutional leadership. We recognize that institutional leadership faced—and continues to face—incredible challenges requiring rapid response to changing conditions while balancing the interests of numerous stakeholders. We do not claim to have definitive answers for how to rank and prioritize workforce morale while meeting these challenges. However, in what follows, we will argue that (1) morale is an independently valuable good that must be weighed and balanced against other goods and (2) a necessary condition for fully realizing any other goods that depend on high quality team-based care. As such, any response to the pandemic that disregards or negatively impacts morale will not only be ethically suspect, but also less effective than it would otherwise be in achieving whatever goals it might prioritize above morale.

While it is generally easy to recognize (low or high) morale, particularly when one is a part of the group experiencing it, it is more difficult to actively cultivate it. It will be helpful, then, to first briefly consider the nature, value, and determinants of morale within healthcare institutions. Morale is a multifaceted, longitudinal, and relational experience that individuals share when they identify with and contribute to certain kinds of collective activities (most often defined by meeting challenges or facing opposition or hardship together). Morale is *relational* in that it pertains only to certain groups of persons rather than to isolated individuals (it would probably be a mistake to speak of a hermit's morale rather than his spirit or mood). Morale is *longitudinal* in that it develops and evolves over time and across contexts; it has a distinctive history against which present experiences are comparatively indexed (e.g., "the morale of the unit is improving [or declining]"). Finally, morale is

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