Vulnerability and Clinical Research: Mapping the Challenges for Stakeholders

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Abstract

Beyond what are characterized as Special Populations in U.S. FDA regulatory considerations is vulnerability of patient populations in a broader context of international guidance. Such a review suggests a rich appreciation for the diversity of patients. Vulnerable patients' status and the associated patient protections are of growing interest in the clinical research environment. To participate in the current developments and reflections, we selected 12 international & recognized core documents that are discussing human research protections and identify all references to them pertinent to Vulnerables. This allows the identification of 15 different categories of Vulnerability, that we group in five kinds of challenges. We then map significant regulatory and ethical interpretations and their implications toward applying what Vulnerability constitutes for the stakeholder ecosystem and its evolving direction as part of the overall protection for patients, defined as a “chain of protection.” Different levels of understanding are proposed: Who are vulnerable (a ‘macro’-mapping), what is Vulnerability (a ‘meso’-mapping) leading to applications with practical questions (a ‘micro’-mapping). We offer this analysis and mapping for practical benefit to a range of stakeholders with staffs whose functional responsibilities indirectly or directly essentially touch the broad spectrum of involvement with patients. The practical application is for multi-stakeholder consideration of patients-as-subjects in research, especially for Sites and Ethics Committees/IRBs, given the extended efforts of “patient-centricity”—the ‘how’s’ and ‘what’s’ of including patients in the clinical research process from discovery to RWE and its implications. Also considered is the value of education and training purposes on the true diversity of patients so that sensitivity to such matters from protocol development through informed consent and privacy protections are taken into account in the era of “new science,” technological advances, and expansion of clinical research investigators, patient populations, and types of non-traditional research sites.

Keywords Vulnerability · Patient protection · Ethics · Clinical research · International core documents

Introduction

For good reason there is growing global concern to involve patients more directly and thoroughly in clinical research notwithstanding confusion over what constitutes patient centrality, patient engagement, patient empowerment, or other ascriptions.

Including, but well beyond recruitment and retention, is engaging with patients from protocol development through safety considerations to valid data and post-approval real-world evidence (in its various modalities of collection) [1].

Impacting essential clinical trial processes and research stakeholders' decision-making also are considerations of—as well as defining and understanding—Vulnerability, including Diversity, of patients—which the authors address in this Commentary. In a more thorough understanding, Vulnerability addresses Diversity and its challenges as is evident in the essential regulatory and ethical interpretations and their implications here compiled and reviewed.

The authors ‘map’ significant regulatory and ethical interpretations and their implications toward applying what Vulnerability constitutes for the stakeholder ecosystem, its evolving direction as part of the overall protection for

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patients (that we defined as a “chain of protection”), and in light of momentum toward formal accreditation of research sites.

We selected as a starting point 12 international & recognized core documents that are discussing human research protections and identify all references into them pertinent to Vulnerables, that allow us to identify 15 different categories of Vulnerability, that we propose to group in five kinds of challenges. We also investigate a few other documents from National Medicines Agencies or Professional organisation that present more practical aspects on clinical research, for the presence of specific information on Vulnerable populations.

The authors offer this analysis, ‘mapping,’ and proposals to inform training and development insights for a range of stakeholders with staffs whose functional responsibility includes any relation to the spectrum of patient involvement; no less, to assist the current CIOMS Working Group XI dedicated to “patient involvement in development and safe use of medicines.”

‘Mapping’ Vulnerability considerations can be done by leveraging in different ways those essential interpretations and their implications toward applying what it constitutes:

- For the stakeholder ecosystem;
- Its evolving direction as part of a stakeholder “chain of protection;” and
- Given the building momentum for voluntary accreditation of research sites, that aligns with the accreditation of Ethics Committees/IRBs together supporting to human research protections.

This “mapping” approach goes beyond a comparison/contrast of seminal documents. It also involves identifying levels of understanding who are vulnerable (a ‘macro’-mapping) and what is Vulnerability (a ‘meso’-mapping) leading to applications (a ‘micro’ -mapping) for the range of research stakeholders.

Background Context

While the FDA re-addressed Vulnerable Populations in terms of inclusion/exclusion criteria (particularly taking into account the age spectrum from birth to aging, pregnant and

lactating women, as well as patient involvement in 2018) [2], Vulnerability is more expansive as a challenge in clinical research for all stakeholders especially in light of Sponsors, CROs, Regulators, Ethics Committees, and Sites trying to understand better and implement “patient-centric” and “patient engagement” measures [1]. Also to consider is that while there is stakeholder appreciation that many critical documents (such as an informed consent and patient leaflet) meet standards of health literacy, such documents are not customized accordingly to meet the needs of the vulnerable [3]. Paradoxically, the vulnerable are not a priority for inclusion in research, yet their participation is so necessary to gain important information to reach a balanced opinion about benefit:risk.

Historically, the first point of the 1947 Nuremberg code [4] explained that the “person involved should have legal capacity to give consent” and most of the significant international human research protection documents thereafter have paid specific attention to vulnerable subjects participating in clinical research.

Here, based on our literature review, we selected as a starting point 12 international core documents that are discussing human research protections [4–15]. Our analysis of them provides 15 different categories of Vulnerability—appreciating that a person may be vulnerable in more than one way. From a scientific perspective, Vulnerability now also needs to embrace those suffering from disease states not given enough attention, emergency situations, and complex co-morbidities (somewhat addressed in the 2018 FDA Working Report in terms of product effectiveness and safety) [2], as well as incurable or terminal situations. In brief, the scope of vulnerability has increased; and understanding Vulnerability in all its expansive contexts is confounded by the ultimate challenge and its implications for all key research stakeholders: Who is not vulnerable?

The Macro Map: Who are Vulnerable?

Our review of the literature identified 12 main core international human research protections documents (from the 1947 Nuremberg code to the recent 2016 CIOMS International Ethical Guidelines for Health-related Research Involving Humans): [4–15]

Title of the Document	Authors/Organization	Date of Issuance/Current Date of the Document Used
The Nuremberg Code	Nuremberg Military Tribunals	1949
The Belmont Report	US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research	1979
Annex 3, Guidelines for good clinical practice (GCP) for trials on pharmaceutical products	WHO	1995
The Convention for the protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine (Oviedo)	Council of Europe	1997
The WHO Handbook for good clinical research practice (GCP): Guidance for implementation	WHO	2002
International Code Of Ethical Conduct for Pharmaceutical Physicians, International Federation of Associations of Pharmaceutical Physicians	IFAPP	2003
The UNESCO Universal Declaration on Bioethics and Human Rights	UNESCO	2005
The Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research (Strasbourg)	Council of Europe	2005
The WHO Standards and Operational Guidance for Ethics Review of Health-Related Research with Human Participants	WHO	2011
The World Medical Association (WMA) Declaration of Helsinki	World Medical Association	2013
The International Council For Harmonisation Of Technical Requirements For Pharmaceuticals For Human Use (ICH) Integrated Addendum To ICH E6(R1): Guideline For Good Clinical Practice E6(R2)	ICH	2016
International Ethical Guidelines for Health-related Research Involving Humans, Prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO)	CIOMS/WHO	2016

Our analysis of them identified the 15 different categories of Vulnerability that are presented below:

1	People living with disabilities, multiple chronic conditions, or faced with physical frailty, for example, because of age and co-morbidities
2	Patients with incurable diseases or terminally ill patients
3	Patients in emergency situations
4	Ethnic and racial minorities
5	Homeless persons, nomads, refugees, or displaced persons
6	People living in an authoritarian environment, military service personnel, people deprived of liberty such as prisoners or confined (nursing homes or institutionalized persons)
7	People economically disadvantaged, living in a community in low-resource settings, unemployed or impoverished, or receiving welfare benefits or social assistance
8	People politically powerless, marginalized, stigmatized, or facing social exclusion or prejudice
9	People incapable of giving consent, or with limited capacity to consent, persons with diminished autonomy, those lacking freedom to consent or to decline to consent, persons who have a mental disorder or persons relatively (or absolutely) incapable of protecting their own interest
10	People educationally disadvantaged, unfamiliar with modern medical concepts and clinical trials
11	People who perceive participation as the only means of accessing medical care, those for whom the research is combined with care, or those that may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation
12	People in a dependent relationship with a physician, at risk of undue influence of hierarchical structures or easy to manipulate
13	Minors, or the immature
14	Women, pregnant women, breastfeeding women, human fetuses, embryos, and neonates
15	Vulnerability related to gender, sexuality, HIV serostatus, or other stigmatizing conditions

These 15 categories are very heterogeneous, can overlap, and most of these vulnerabilities need to be managed and considered in different ways. One cannot simply apply the same protection mechanisms to a minor, a terminally ill patient, persons who have a mental disorder, or a member of a minority community.

Within these categories are clearly references to Diversity in both its narrow and broader senses. Yet, in the context of Vulnerability typically referenced terms relating to Diversity (in particular, “underrepresented” and “racial minorities”) [16] do not suffice to address compounding barriers impacting inclusiveness to achieve both societal and scientific goals.

For overall stakeholder considerations, underlying this span of vulnerabilities and Diversity, we define five kinds of challenges with some applying to more than one of the above categories. The fundamental value for doing so is to provide stakeholders ranging from Sponsors through Sites to Ethics Committees/IRBs with a means to consider the matter from protocol development through ethical and regulatory oversight to execution of the study.

for Pharmaceutical Physicians, International Federation of Associations of Pharmaceutical Physicians [IFAPP] [9]. While the elderly can be mapped to several of the categories identified, they are not specifically mentioned as a vulnerable population in the other major human research protections documents that we have selected.

Further formal consideration also needs to be given to ranges of ages in the elderly in relation to possible or probable vulnerability. Gerontologists and elder care professionals can provide important and necessary insights. The spectrum of cognitive decline through ranges of dementia impairing an informed consent decision is probably the most evident and the most frequent identification criterion for this patient population as impacting Vulnerability [17].

The elderly have not been absent from the research landscape (FDA, EMA, ICH, among others have Guidelines or Working Groups), but all recommendations/guidances have been developed to promote specific clinical trials and/or inclusion of elderly into them. [18–20] Their Vulnerability has not been a topic of concern into them.

(A) Control, or power/-less challenges

- 5. Homeless persons, nomads, refugees, or displaced persons
- 8. People politically powerless, marginalized, stigmatized, or facing social exclusion or prejudice
- 11. People who perceive participation as the only means of accessing medical care, those for whom the research is combined with care, or those that may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation
- 12. People in a dependent relationship with a physician, at risk of undue influence of hierarchical structures or easy to manipulate
- 13. Minors, or the immature

(B) Chronological, or demographic-related challenges

- 13. Minors, or the immature
- 14. Women, pregnant women, breastfeeding women, human fetuses, embryos & neonates

(C) Coercion, or inducement-prone challenges

- 1. People living with disabilities, multiple chronic conditions or faced with physical frailty, for example, because of age and co-morbidities
- 2. Patients with incurable diseases or terminally ill patients
- 3. Patients in emergency situations
- 6. People living in an authoritarian environment, military service personnel, people deprived of liberty such as prisoners or confined (nursing homes or institutionalized persons)
- 7. People economically disadvantaged, living in a community in low-resource settings, unemployed or impoverished, or receiving welfare benefits or social assistance
- 11. People who perceive participation as the only means of accessing medical care, those for whom the research is combined with care, or those that may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation

(D) Capacity challenges

- 9. People incapable of giving consent, or with limited capacity to consent, persons with diminished autonomy, those lacking freedom to consent or to decline to consent, persons who have a mental disorder or persons relatively (or absolutely) incapable of protecting their own interest
- 10. People educationally disadvantaged, unfamiliar with modern medical concepts and clinical trials
- 13. Minors or the immature

(E) Culture challenges

- 4. Ethnic and racial minorities
 - 10. People educationally disadvantaged, unfamiliar with modern medical concepts and clinical trials
 - 15. Vulnerability related to gender, sexuality or HIV serostatus, or other stigmatizing conditions
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Additional Observations

Surprisingly, reviewing these core international documents revealed an absence of reference to the elderly population except in the International Code Of Ethical Conduct

In addition to the elderly, there is another key patient population largely not mentioned in the 12 core documents we selected: With the exception of the 2003 International Code Of Ethical Conduct for Pharmaceutical Physicians [9] & the 2016 CIOMS International Ethical Guidelines for

Health-related Research Involving Humans [15], patients affected by rare diseases are not mentioned as a vulnerable population in the core documents we selected. Interestingly, even if rare disease patients are not largely considered a vulnerable population, we think they probably contribute the most to the fight against group exclusion from research via their patient associations.

A key element common to these rare disease patients is motivation for R&D on their own disease and on rare diseases in general. For years, this motivation faced a lot of ethical and practical challenges (Limited number of sponsor & research funding, small or very small patient population for recruitment in each country, divergent landscape of clinical trial regulations, challenge in data collection). Some inherent challenges (incomplete understanding of disease pathophysiology or of the natural history to inform trial design) also limit the setup of clinical trials. For a few decades, the trend is in the opposite direction, mainly due to the development of powerful international or national associations [21, 22], the creation of Program/Department at National Agency level [23, 24], and an increased interest from the Pharmaceutical industry.

A re-emerging type of Vulnerability is associated with compensating healthy volunteers especially in developing countries for participating in safety or bioequivalence studies. The financial incentives become so attractive for poorer populations that individuals volunteer to participate in more than one trial, whether serially or simultaneously, becoming as if “professional healthy volunteers” put their health and clean data at risk [25].

The topic is not new, and some developed countries had put in place registries of Phase 1 healthy volunteers several years ago in response [26]. Now, this phenomenon of ‘trial hopping’ looms so large for trials demonstrating bioequivalence of generics that CIOMS is proposing in their September 2018 newsletter the creation of a new Working Group for “Protecting healthy volunteers in clinical trials” to encourage research into this poorly documented field and to make recommendations [27].

Another—if subtle—aspect of Vulnerability relates to a recent article reporting that as high as 75% of participants withheld information to avoid exclusion from studies [28]. This creates the specter of Vulnerability once a patient has been included in a clinical trial. Vulnerable patients (our category#11: “People who perceive participation as the only means of accessing medical care, those for whom the research is combined with care, or those that may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation”) will typically be subject to this double Vulnerability—for inclusion in the trial as well as to stay in the trial.

The Meso Map: What is Vulnerability?

Not all research stakeholder roles routinely and regularly entail confronting the matter, so understanding what has been the formally defined terrain of Vulnerability can be useful to appreciate what is involved in making sensitive collaborative decisions. That said, however, the evolving understanding of Vulnerability, as suggested earlier, suggests what has been understood traditionally is not enough.

While Vulnerability was initially defined in 1947 for each human being as an individual (Nuremberg code) [4], this had continued to be the case mainly due to the absence for a few decades of other documents on the topic, based on our own literature review.

Even with the development of Good Clinical Practices initiated by the World Health Organisation (WHO) in the late 1960s, the protection of the vulnerable patient moved for the first time in a different direction with the AIDS Research, Guidance for IRBs [29] and its focus on confidentiality being considered as a particularly sensitive aspect of AIDS research and from the perspective of the rights and welfare of the subjects in particular.

It is interesting to note that the major health event that was the AIDS epidemic at the end of last century and the resultant imperative to reduce mother-to-child transmission of HIV required engaging pregnant women appropriately in clinical research so that they can make decisions based on evidence-based medicine [30].

Until this, the unanticipated complications from utero exposure to thalidomide and diethylstilbestrol, the FDA policies protecting female research participants of reproductive age from exposure to teratogens were interpreted as a mandate to exclude pregnant women from clinical trials [30].

It is important to highlight that in ICH E6(R1) (1.61 Vulnerable Subjects) [14]—and before research subjects incapable of giving personal consent—the first vulnerable group identified is actually clinical trial-associated personnel (such as medical, pharmacy, dental, and nursing students, hospital and laboratory personnel subordinate to research principals, and employees of the pharmaceutical industry) that correspond to the Coercion category we proposed.

With evolving understanding, the concept of “Vulnerability by default” emerged as seen in the 2002 WHO Handbook for good clinical research practice (GCP): Guidance for implementation: [8] “In general, all individuals, including healthy volunteers, who participate as research subjects should be viewed as intrinsically vulnerable.”

More recent Guidance notes that seriously ill or vulnerable populations “may require more intensive monitoring and consideration of on-site monitoring visits to be sure appropriate protection is being provided” (FDA Guidance

for Industry Oversight of Clinical Investigations, A Risk-Based Approach to Monitoring) [31].

After 5 years of this Guidance, several questions arise as to the sufficiency of its impact:

- Will clinical trials including vulnerables now be the last involving intensive “classical” monitoring; and
- Will on-site monitoring now be focused largely on patient protection to the minimization of other important topics like data quality?

No less significantly:

- What will the impact of remote monitoring be on observing vulnerability?

The most recent version of the CIOMS International Ethical Guidelines for Health-related Research Involving Humans, [15] released in 2016 redefines the concept of Vulnerability in contrast to the “traditional approach to Vulnerability in research to label entire classes of individuals as vulnerable” and to avoid “considering members of entire classes of individuals as vulnerable.”

Previous approaches to Vulnerability simply excluded a class of vulnerables completely from research. The unintended consequence of this kind of ‘as if’ paternalism is that exclusion of a group of vulnerables leads to a scarcity of evidence on the diagnosis, prevention, and treatment of diseases that affect them [30]. Moreover, it causes an ethical paradox in that placing vulnerable subjects in exclusion criteria means they are excluded from the benefit:risk assessment at the time of license approval so that they end up in ‘missing information’ in the risk management plan and may fall into the category of ‘off label use.’ While convenient for the legal process of licensing, it does not aid public health interests of the Vulnerable.

Now, the CIOMS guidelines promote the opposite approach and emphasize that “the exclusion of especially vulnerable populations must be justified” or that “the adults who are not capable of giving informed consent must be included in health-related research unless a good scientific reason justifies their exclusion.” [15] This is also addressed, in part, in the 2018 FDA Working Report [2].

It is also noteworthy that nothing new was added in the addendum to ICH E6(R1) about the range and intrinsic variability of vulnerable people excepting a vague general reference relating to quality management. Will the topic be taken into consideration as part of the ongoing “GCP renovation” effort within the coming revision of ICH E6 and possibly E8 (2.1 Protection of clinical trial subjects)?

Finally, the 2012 European Medicines Agency (EMA) Reflection Paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside

of the EU/EEA and submitted in marketing authorization applications to the EU Regulatory Authorities [32] offers the following range of terms:

Vulnerable subjects, poorly educated subjects, illiterate subjects, Vulnerability of person due to poverty, lack of adequate health care systems or lack of access to medicines, vulnerable population or community, vulnerable group, vulnerable categories & vulnerable individuals.

While this is in line with the expansion of previous definitions of “classically” vulnerable populations or communities, it also moves toward a broader one, considering that everyone can at a certain point of time in his or her life be vulnerable—circumstance Vulnerability, also referred to as “situational Vulnerability.”

A “Chain of Protection” & the Micro Map

Reviewing core documents identifies a series of similar terms on how to deal with Vulnerability, ranging from special attention, specific consideration, and protective additional conditions to extensive protection. But what is essential to emphasize is that protection of vulnerable subjects in clinical research is a responsibility of all who have contact (indirectly as well as directly) with a patient considering participation in clinical trials. That constitutes a “chain of protection” which can be informed by our mapping that includes:

- the Sponsor, for a Vulnerability-sensitive approach to research protocol development including but not limited to inclusion/exclusion criteria and real-world applicability;
- the CRO, for a similar Vulnerability-sensitivity approach in its delegation from the Sponsor, especially in the message delivered to the investigational sites;
- the Ethics Committees (IRBs/IECs), for reviewing the protocol, the patient population, and the recruitment process for Vulnerability potential; and
- the Investigational Site, for specific processes and procedures to address Vulnerabilities.

Such a “chain of protection” is typically addressed indirectly in SOPs of each of these stakeholders and based on the view of groups of vulnerables—focusing on a “culture of compliance” as opposed to a more embracing “culture of conscience” that would address the needs of all stakeholders more thoroughly.

Of course, circumstances of a particular study may well also dictate that consideration—by all stakeholders, not left to the Ethics Committee alone—be given to the potential

for individual vulnerabilities beyond the ‘boilerplate’ SOPs. Particular study circumstances can be addressed prior to and during site qualification, investigator training, as well as study start-up processes.

Sponsor research protocols are a good place to begin to address day-to-day operational dimensions. They devote considerable space to the specific scientific and statistical eligibility and exclusion criteria of subjects as well as the ethical criteria for eligibility being largely limited to whether or not the subject or a legally authorized representative may give consent. Motives for participating are rarely, if ever, directly addressed. They include, for examples, unrealistic expectations or emotional and psychological suitability.

The recent NIH-FDA Clinical Trial Protocol Template [33] that will be used in the development of a large number of studies, takes Vulnerability into consideration with mention in the contexts of strategies for Recruitment and Retention, Adverse Events and Serious Adverse Events, as well as in the Consent Procedures and Documentation sections. However, there is a danger that in the way it is presented, Vulnerability is treated more as a barrier that has to be overcome rather than considering vulnerability as valuable to research.

The TransCelerate BioPharma Common Protocol Template [34] that will also be used in the development of a large number of studies is more formal—that is, explanatory of the process itself—hence not directed toward subject (vulnerable or not) protection as such. It is only with the current Template v6.0 that a reference to vulnerable study population was added in the Scientific Rationale for Study Design (chapter 4.2).

While scientific rationale for including a vulnerable subject population is important, it is not the only factor in considering inclusion of such populations. There are also rationales from social justice and ethical considerations to be taken into account.

Another more surprising element where the protection of the vulnerable is notably absent is in Guidance or Guidelines (FDA, EMA) protecting patients or describing the clinical development of medicinal products for the treatment of particular disease affecting them. Examples include:

- The FDA “Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials Guidance for Industry (rev1)” [35] which does not discuss the Vulnerability from the point of view of pregnant women.
- The Oct09 FDA Guidance for Industry “Investigator Responsibilities—Protecting the Rights, Safety, and Welfare of Study Subjects” [36] which also completely lacks Vulnerability considerations.
- The EMA Guideline on the clinical development of medicinal products for the treatment of Autism Spectrum Disorder (ASD) [37], which contains nothing on patient

protection and related ethical questions with the exception of a one line reference to the ethical considerations for clinical trials conducted with the pediatric population.

These documents focus on the technical aspects of product development, while addressing patient protection implications only in passing.

Turning to other key stakeholders, the mechanisms protecting the Ethics Committee from influence are more detailed and systematic than those protecting vulnerables themselves. Similarly, documents addressing the research protocol (such as described in “The WHO Standards and Operational Guidance for Ethics Review of Health-Related Research with Human Participants” [12]) emphasize “mechanisms to insure independence of REC operations in order to protect decision-making from influence by any individual or entity that sponsors, conducts, or hosts the research it reviews.”

At the investigational site, Vulnerability protection is immediate, and the one that generates the most variability even at the same site. It is the least adequately harmonized and documented. Here—to return to a topic not very much developed since the Nuremberg code—is the essential matter of the quality of the consent: “The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment.” [4] This is especially true for vulnerables.

All clinical trial personnel involved in presenting the trial or directly involved in obtaining informed consent need to be trained in and pay attention to individual Vulnerability that is clearly subject specific. Situational Vulnerability cannot be protected by the protocol or the Ethics Committee review alone. It is fully a responsibility of the site personnel who are also sensitized to cultural dimensions in their patient communities. An excellent example is given by William J. Heeran, Richard O. White, & Shari L. Barkin in their 2015 article on a clinical trial designed to prevent childhood obesity in a low-income underserved population. In addition to the use of low literacy techniques, visual aids & graphics, the authors mentioned that the study team was trained, to use basic communication techniques, including teach-back techniques, to avoid medical jargon, and to identify child dissenting behaviors [3].

For these research professionals, a difficult part of the process is rejecting a subject from the pool of potential patients after the initial discussion of the trial and any identification of a potential level of Vulnerability. This is especially challenging for trials featuring a vulnerable population or for any trial with recruitment delay—a large proportion of all trials conducted.

Here, as elsewhere in determining the value of defining and inclusion or not of vulnerables, there may be also a role

for Data Safety Monitoring Boards if acting sooner—in ‘real time’ in the process—rather than later.

Subject recruitment is framed by inclusion and exclusion criteria. Most are disease specific and few take sufficiently into account in the design protecting vulnerable subjects. This puts the responsibility on site staff to make personal interpretations. Such interpretations need to be supported by both directly pertinent training and site procedures for recruitment, retention, and Vulnerability detection/evaluation.

The two notions of Competence and Level of Understanding commonly used in the recruitment process of patients in pediatric clinical trials, as described by the Nuffield Council on Bioethics [38], can also be taken into consideration for other vulnerables. This leads to the associated notion of “acceptable Vulnerability” that needs to be evaluated for each potential trial participant.

Finally, the last sentence (point 3) of the Additional Protocol to the Convention on Human Rights and Biomedicine concerning Biomedical Research [11] is extremely important and practical aspects of it need to be further investigated. It reads: “Where the capacity of the person to give informed consent is in doubt, *arrangements* shall be in place to verify whether or not the person has such capacity.” Accordingly:

- Are such arrangements addressed in SOPs or other operating processes such as those for inspections and audits to address their quality in order to align better Compliance with the needs of the vulnerable?
- What might the range and sufficiency of them be (e.g., Cognitive or other objective measurements and tools; the presence of a legally authorized representative or equivalent, other approaches—depending, of course, on the Vulnerability).

Moving Forward: Proposals & Conclusion

Compiling this research and analysis leads to practical proposals in dealing with and managing Vulnerability: Proposals impacting not only where the patient meets the clinical research enterprise at the research site (and in light of momentum building for voluntary site accreditation), but also for the enterprise as a whole.

As such, this research and analysis can provide a foundation for further understanding, education, and direct implementation.

Given the essential matter of who is and who is not vulnerable, there are different vantages to be taken into account:

- To organize a basic understanding, there are at least 15 categories collated from seminal international human research protection documents; as well as five types of

challenges: Control, Chronological, Coercion, Capacity, and Culture.

- The 15 categories are very heterogenous and most of these Vulnerabilities need to be managed and considered in different ways. One cannot simply apply the same protection mechanisms to a minor, a terminally ill patient, or persons who have a mental disorder.
- There are the realities of Circumstance Vulnerability, Situational Vulnerability, and the Temporality of Vulnerability (permanent or temporary) as mentioned in 2016 CIOMS International Ethical Guidelines for Health-related Research Involving Humans [15].
- Toward an evolution of Vulnerability management, the above CIOMS Ethical Guidelines rejecting the group approach to vulnerability moves in an appropriate direction: Development of a personalized vulnerability.

In addition—keeping in mind an operational vantage and the value of inter-disciplinary perspective—consideration of Vulnerability can and should include:

- Scientifically focused Vulnerability—to assure cohort validity;
- Social Justice-focused Vulnerability—to assure population inclusiveness;
- Ethics/Patient Empowerment-focused Vulnerability—to assure not only fundamental ethical principles are observed but also Human Factors insights are considered; and,
- Social Science-focused Vulnerability—to assure cultural differences are taken into account qualitatively and quantitatively.

Applied to traditional thinking about Diversity, for example, all four aspects of Vulnerability can guide initial stakeholder planning. Then, more robustly, the range of those who are vulnerable (as depicted earlier in the “Macro” mapping) can be considered in order to refine the recruitment and retention strategy and implementation.

In brief, there is clearly need for further consideration, discussion, and action throughout the clinical research enterprise toward basic awareness, professional training and development, and safety, risk management, and mitigation.

Basic questions can serve as a framework and starting point—not only for considerations of the site team but also for each stakeholder representative in the decision-influencing process of the “chain of protection:”

- Does the research setting minimize or enhance Vulnerability? Diseases are intimidating, causing even the most courageous individuals uncertainty. Research professionals and their facilities can easily be daunting. If

the non-vulnerable find this to be so, how much more do the vulnerable?

- Are there support structures in place for the vulnerable person—aside from the research team—who can assist the person in getting enough information, achieving an appropriate level of understanding, and being able to participate voluntarily (as well as being able to withdraw)?
- Does the discussion of the research and the informed consent process take into account factors that render an individual temporarily vulnerable and take appropriate steps to mitigate those factors?
- Has the person participated in trials before? And, if so, for what reason(s) and how long ago?
- Does the person really need to be in the study? And, if ‘no’ because of other therapeutic options, does the person know those other options?
- Does the person really know the difference between research and treatment? This appreciation needs to extend beyond the range of potential risks; and a fundamental understanding that the goal is gathering “clean data” not typical healthcare.
- Are there underlying factors that are excessively influencing the individual’s participation? These factors might well include physical and/or economic desperation.

Other operationally oriented suggestions are:

- SOPs addressing Vulnerability—SOPs for each of the stakeholders in the “chain of protection,” which can include identification of specific measures of protection for the categories of Vulnerability we have defined. To our knowledge, the concept of what risk-based vigilance means in the context of individual vulnerability has not been discussed.
- Development of learning and education for those dealing with issues of vulnerability—and as a basis for a training curriculum that would be an element of site accreditation.
- Development of subject Vulnerability assessment tool(s) useful to define for each potential research participant an acceptable level of Vulnerability compatible with his/her research participation. This would also help to identify vulnerabilities that are not readily apparent. Clearly any such scale needs to be collaboratively designed, tested, and inclusive of subject matter—and inter-disciplinary—experts including social scientists (sociologists and anthropologists).
- Active engagement of these same social scientists in considering Vulnerability matters not limited to their role in developing “subject Vulnerability assessment tools.”
- The systematic addition of an inclusion criteria about Vulnerability management in research protocols. Because

Vulnerability can affect everyone, this proposal cannot be limited to protocols on identified vulnerable populations.

- A collaborative Informed Consent process involving more than one of the site team with the subject/patient and his/her friend, family member, legally authorized representative, and/or a patient advocate familiar with Vulnerability in a clinical research setting. Note that not all need to be physically present in order to conduct this collaborative process.
- A systematic reflection period built into the protocol design and sequence of events flow chart placed between the presentation of the clinical research and the actual signature of the informed consent form to participate by the patient.

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Conflict of interest

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