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Excluded, not dismissed: enhancing benefit in clinical research

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Abstract

Participation in clinical research projects may allow an opportunity for early detection of covert diseases and subclinical disorders in asymptomatic volunteers from study-specific screening process. Exclusion of a potential participant due to failure to meet inclusion criteria eliminates any possibility of potential for research related benefit, as may exist for those that are deemed eligible and allowed to proceed with participation in the specific research study. Although the institutional bodies overseeing conduct of clinical research strive to ensure an ongoing scrutiny and prioritization of participants' wellbeing, we perceive that these mechanisms fall short as regards the interests of those volunteers who are subsequently excluded from participation in clinical research of relevance. While provision of ancillary care to address health concerns that are unmasked during the screening process may be an optimal strategy, the likelihood of successfully implementing this latter concept in current times of fiscal constraints is slim to nonexistent. Through this submission, we hope to initiate a dialogue within the research community regarding whether the current paradigm of conduct of clinical research be modified to include some degree of consideration for the *screened out*. We herein propose that for those volunteering for disease/disorder specific clinical research, some added degree of benefit can be assured to the *screened out* population through the provision of targeted health education or counseling.

Keywords

Ethics; clinical research; eligibility criteria

CASE

A 23-year-old obese woman with irregular menses responded to an advertisement seeking volunteers for participation in a research study on a common endocrinopathy of reproductive years, polycystic ovary syndrome (PCOS). PCOS is a recognized risk for chronic disorders

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Ethics Approval: The study was approved by the Human Investigation Committee, Yale School of Medicine and written consent was obtained.

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such as diabetes and cardiovascular disease (CVD) [1]. This interested potential participant, however, was deemed ineligible for the specific study due to evidence of blood pressure elevation consistent with hypertension, a pre-specified exclusion criterion. The study recruitment proceeded uneventfully to completion. A review of the enrollment process by the research team identified existence of pre-morbid and potentially treatable health concerns in a substantial proportion of the *screened out*. The clinician researcher herein voices a realization of missed opportunities for targeted preventive care strategies to a potentially receptive population whose health concerns became evident during the research-related screening process.

WHY FOCUS ON THE *SCREENED OUT*?

The goal of clinical research is two-fold: to produce generalizable knowledge, and in doing so, to better the health of individuals and communities. To this end, although possibly a skewed sample, the health profile of the *screened out* individuals may reflect to some degree, the overall health of a community. While the enrolled population has the potential of benefiting from participating in the research study itself, the authors herein raise a question whether overall health benefits of clinical research for the community at large could be broadened through targeted interventions in the *screened out* population. This concept may be particularly pertinent for individuals whose *at-risk* status gets unmasked in the course of research related screening, as exemplified in the index case.

Expanding upon the goals of clinical research to incorporate a focus on the *screened out* holds a potential for enhancing the researcher-community relationship; such a strategy may increase the likelihood of community participation in future clinical research. In a population of young women diagnosed with PCOS who are deemed at risk for long-term morbidities including CVD and diabetes, we briefly introspect on the clinician researcher's many roles extent of responsibilities. Clinician researcher's interactions with research participants, *screened out* as well as *screened in*, can be construed as opportunities for implementing preventive care concepts and for impacting on an individual's perceptions relevant to overall health. A potential for benefit is believed from a timely dispensation of bare minimum preventive care strategies to potentially *at-risk* populations. Targeted counseling (relevant to the disease/disorder under study) if made available to all volunteers including those *screened out*, by improving disease/disorder specific understanding at the individual level, may to some degree address the health related perceptions and needs of a community.

INVESTIGATOR'S ROLE: RESEARCHER OR CLINICIAN?

Most clinicians and clinical researchers agree that since research and clinical care have distinct aims and methodologies for attaining the respective goals, the two concepts operate under distinct ethical frameworks [2,3]. While the clinician's responsibility lies in ensuring and providing care for his or her patients, the researcher's focus lies in the scientific advancement of the field [3,4,]. For a clinician researcher however, the boundaries of these responsibilities towards the individual subject/patient, the community and to scientific quest may at times be subject to ambiguity [3]. In their arguments, Richardson and Belsky propose an ethical framework of ancillary care (i.e. not necessarily research related) in efforts to guide clinicians in achieving equipoise within their roles as researchers [5]. The authors suggest "a partial and limited entrustment of participants' health to researchers" that varies in scope and strength depending on the context of the study. A greater moral obligation on the clinician researcher than non-clinician investigators is implied due to the former's ability to affect the medical welfare of patient subjects who they may deem as *vulnerable*; these

arguments however were neither implied for nor considered in their applicability to the *screened out*.

RESEARCHER'S RESPONSIBILITY TOWARDS THE SCREENED OUT?

Participant vulnerability and researcher's responsibility are unequivocally accepted as governing principles for the conduct of clinical research [4, 6-7]. Pertinent to the argument at hand however is that in the current paradigm, concerns for subject vulnerability and researcher's responsibility towards ensuring research subject's wellbeing are exclusively geared for the enrolled; any consideration regarding potential vulnerability of the *screened out* is non-existent, and disappearance of the *screened out* off the research team's radar an accepted practice. Should a research subject who, after having negotiated the informed consent process, is *screened out* due to an underlying and hitherto undiagnosed and now unmasked (due to screening specific tests) disease or disorder (as evident in the index case), not reflect some degree of vulnerability? be perceived as *vulnerable*? What *degree of dependence*, if any, does the *screened out* population have on the researcher? Should the researcher be held to ensure a minimum level of benefit for the *screened out* and if so, would this ancillary responsibility impose a *burden* on researchers' finite time and resources?

It is evident that at minimal, research subjects do willingly entrust some measure of their wellbeing to the clinical researcher; the clinician researcher, by accepting this trust, takes on a commensurate level of responsibility towards all volunteers, including those subsequently *screened out*. In their work on the issue of providing antiretroviral therapy in HIV/AIDS research, Richardson proposes that the patient-researcher relationship be classified according to the *degree of involvement*. In a gradation system, those *screened out* were considered to have a relationship of "minimal depth" with the researcher [8]. This is contrasted to relationships of "high depth," involving more extended periods of interaction between the subject and researcher. In these relationships, the author deems it appropriate for researchers to provide ancillary care to the research participants. While the relationship with screened out individuals are of "minimal depth", at least in the context of a disease with serious health consequences, the author notably does not place the *screened out* entirely outside the scope of physician's responsibility either. We build upon this understanding to suggest a middle ground for the potential participant who, despite her or his willingness to participate and contribute to the research under study, is deemed ineligible from further participation in a research study that is otherwise relevant to his or her clinical condition/s. Rather than suggest any *obligation* on the part of the clinician researcher for provision of ancillary care to the *screened out*, a shift in perceptions and practices of clinician researchers is advocated to allow maximizing on potential *missed* opportunities for possible benefit for a population that in many situations, may indeed meet criteria for vulnerability, with minimal cost or effort for the research team or institution.

STRATEGIES THAT MAY OFFER BENEFIT TO THE SCREENED OUT WITH MINIMAL BURDEN ON THE RESEARCHER

It is not our purpose to add to an already overwhelming fiscal and administrative burden being shouldered by the clinical researcher as well as the health care system. Provision of appropriate referrals for the screened out for targeted health care services is an option. Given that participation in clinical trials is an opportunity for many underprivileged and uninsured individuals to gain access to free healthcare, in the absence of an existing infrastructure that ensures access to free health care for the under privileged, this approach is unlikely to confer a meaningful benefit [9-10].

A disease centered approach that utilizes the expertise of a clinical team familiar with disease specific risks and sequelae to offer targeted counseling is likely to offer some degree of benefit to all potential participants (enrolled or *screened out* alike). By improving disease/disorder specific understanding through targeted interventions aimed at an individual level, the clinical researchers are poised to positively impact on the health related perceptions of a community. In a 2006 study focusing on PCOS, 68 participants in an ongoing clinical trial were provided at least two supplemental unstructured counseling sessions from a gynecologist and a postdoctoral fellow specializing in reproductive endocrinology on the physiology of PCOS, health risks associated with it, and pharmacological treatments for PCOS [11]. At the end of the trial, these participants were given post trial surveys on the supplemental counseling sessions. The results revealed that “women with PCOS felt empowered to participate in the management of their condition and communicate more clearly with their primary care providers.” Perhaps researchers can use such counseling sessions to similarly “empower” the *screened out* individuals so that they can take control of their risk factors and independently embark on improving their health.

An informational leaflet, while seemingly trivial, has proven to increase patient knowledge and confidence. A study of patients with chronic rheumatoid arthritis showed that providing patients with informational leaflets increased patient knowledge of their disease and “generated a sense of reassurance” [12]. The study also showed that this new knowledge base wasn’t short lived but was maintained up to six months. In addition, researchers found that this increased knowledge from the informational leaflets was not a source of psychological distress as believed by some.

So how does this increased knowledge translate into lifestyle changes? A study in Sweden compared the effect of providing coronary heart disease patients with general knowledge about lifestyle changes to reduce risk factors for heart disease versus providing these patients with information specific to their own health [13]. Coronary heart disease patients who were provided with specific knowledge concerning their individual risk factors, including obesity, smoking, diet and blood pressure were more likely to change their lifestyle to diminish these risks. This study shows that it is possible that by providing specific targeted information we may be able to decrease the health risks of screened out populations.

It is imperative that we clarify that the idea is not for the clinical researcher to take on the role of primary care giver. Nor is our intent to propose absolutes, but to float concepts for consideration and deliberation by the clinical researchers and regulatory bodies alike. Our purpose herein is to suggest that in the context of clinical research, we utilize the opportunity of conveying health-promoting guidelines to a *receptive* population that is sensitized to and interested in the disease/disorder under study. Informative pamphlets, short lectures, or group counseling sessions are options for providing targeted information on issues that are equally pertinent to the *screened out* as to those deemed eligible; such a strategy holds a potential for benefit for all volunteers regardless of the status of enrollment with minimal burden on the existing infrastructure or researcher’s resources. Such an approach is also likely to foster community participation in clinical research ventures, thus translating to benefit all around.

LIMITATIONS

We are suggesting that clinical research be so designed that the act of volunteering offers any potential subject a minimum degree of personal benefit, even if it is simply a better understanding of the pathophysiology and management of the disease under study, and/or familiarity with disease specific preventative strategies, if applicable. Our proposed

paradigm however is untested and our assumption that researchers will be able to identify preventative aspect and modifiable risks within each disease/disorder understudy is simplistic. Successful implementation of the suggested concepts will encroach on researchers time and resources. However, done in a careful manner, seeking to provide a minimal level of benefit for the *screened out* population is an achievable goal that may help to better align the expectations of the potential participant and researchers. Such practice is further likely to foster trust-building between communities and the academics conducting clinical research, thus encouraging community participation in clinical research endeavors.

CASE STUDY

Health concerns were evident in the index case; a 23-year-old obese woman with PCOS was deemed ineligible from participation in a clinical research study [14] due to evidence of previously undiagnosed hypertension, a predetermined exclusion criterion. The individual was informed of parameters that led to her ineligibility and advised to follow up with her primary provider. Many more volunteers were excluded from participation in the study due to their meeting exclusion criteria. It was only at completion of the research project when the research team came to appreciate the concerning prevalence of a spectrum of pre and co-morbidities apparent in the *screened out* population, leading to formulation of the question at hand.

We herein examine how while striving to adhere to the research protocol, we, the clinicians, missed opportunities of potentially impacting positively on the health of a population that in hindsight is identified as vulnerable. In hindsight, encounter with the index case and other *screened out* participants with PCOS was an opportunity to underscore the spectrum of health burden associated with PCOS and to communicate simple and yet effective risk reduction strategies. While the *screened in* population benefited from research related interventions and interactions with the clinical research team, we realize that we lost multiple opportunities of offering targeted counseling of the *screened out* individuals. This appreciation has prompted us to modify our approach for future clinical research projects wherein we propose inclusion of condition/disease specific information to be made available to *all* research participants (enrolled and excluded).

Benefit through this primary care approach may not be limited to the research population and the community. Should a researcher provide such assistance, it is possible that the *screened out* individual may become more receptive to participate in clinical research in the future, knowing that his or her wellbeing may be improved irrespective of the enrollment status.

CONCLUSION

We herein share a recent appreciation of our responsibility to the *screened out* research subjects, and take this opportunity to propose a consideration for some degree of benefit, inherent or implied, to those who eventually are excluded from further participation in clinical research. Rather than propose concepts that are likely to be perceived as burdensome by the researchers, we hope to engage the research community (researchers, overseeing bodies and participants alike) in seeking venues whereby the potential for benefit (individual and communal) from clinical research may be enhanced without adding to the burden of the research community. We believe that within the constraints of time and finance the research community is already facing, some degree of benefit can be imparted through cost efficient and time effective strategies that are of proven efficacy in improving wellbeing of studied populations (such as through provision of informative leaflets, group lectures, and counseling sessions). Although the proposed shift in paradigm asks for a change of mindset

of the researchers and overseeing bodies alike, by promoting community health and researcher-community communication, the potential for overall benefit from this proposition may not be trivial.

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