



HIV, breast cancer and vaccines: what do high-profile cases reveal about stakeholder engagement in research?

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Substantially engaging stakeholders in research involves making extensive changes to the full life cycle of research, from the initial stage of selecting research priorities to the final stages of dissemination and implementation. Recent scholarship has explored logistical and methodological challenges, including the time, training and resources required for engagement. However, inadequate attention has been given to the intended ends or goals of engagement – what do we want engagement to achieve? An examination of historical case studies can yield important insights regarding engagement and its intended ends. Using historical perspective methods, we explore how clarity about the ends of engagement can inform the design of engagement efforts and lead to better outcomes. We present several lessons for improving stakeholder-engaged research.

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Background

Stakeholder engagement is increasingly viewed as a vital component of high-quality research [1]. Federal agencies have made engaging stakeholders a core criterion for funding decisions [2–5]. It is also gaining ground in industry-sponsored research [6–8].

Substantially engaging stakeholders involves the full life cycle of research, from the initial stage of selecting research priorities to the final stages of dissemination and implementation [9]. Recently, considerable attention has focused on logistical and methodological challenges, including the time, training and resources required for engagement [10–12]. However, less attention has been directed at the goals or ends of engagement – what do we intend engagement to achieve [13]? This question is critical for justifying engagement efforts, and for informing their design.

To date, stakeholder engagement has been grounded implicitly in an expectation that

it enhances research, improves patient outcomes and upholds democratic values [13]. For example, the Patient-Centered Outcomes Research Institute has declared that patient engagement both can improve the usefulness of research and has inherent value [14]. These expectations correspond to the ethical justifications of instrumental and intrinsic values; engagement is a means for obtaining another desirable outcome, such as improving the quality, transparency or relevance of research and, simultaneously, a source of value independent of outcomes, reflecting respect for autonomy and the ideal of self-governance [15].

The theoretical underpinnings of stakeholder engagement can be traced to a variety of disciplines. For example, ecological economics has proposed the normative theory of ‘postnormal science’, which advocates for a ‘democratization’ of science and for ‘broadening of the scientific practice from the traditional (scientific) peer community

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to the extended community of peers' [16]. Stakeholder engagement is also consistent with various democratic theories within political philosophy, reflecting a commitment to citizen participation and creating opportunities for learning and constructive input into decision-making.

Although considerable enthusiasm exists for stakeholder engagement, contemporary engagement efforts are varied [11], rarely if ever evaluated [13], and success is considered differently across involved parties [16]. Optimal practices have been prescribed, but their effectiveness is as yet unfounded [1]. To arrive at a better understanding of what can and is being achieved through stakeholder-engaged research, the research community needs a clear articulation of engagement's ends; why engage stakeholders in research? Specific goals may differ across contexts, but several themes are likely to be shared across many projects, including good stewardship of public resources, improved research, assurance that research is relevant for decision-makers, improved uptake of evidence and, ultimately, improvement in healthcare and overall health. For each research agenda, clearly articulating goals will provide a framework to evaluate success and inform improvement. The critical policy question is whether engagement efforts are reaping the desired outcomes, so defining these outcomes is the first step.

We examine historical examples of stakeholder-engaged research from the past three decades to explore these issues. Our goal is to inform the design and practice of current engagement efforts to align with intended outcomes.

Historical case studies

Historical perspective is a methodology to understand current events based on those of the past [17]. It reflects the belief that examining the evolution of a process and its key players can improve understanding of contemporary circumstances. It employs a longitudinal view of situations, integrating past events to inform current contexts. Using historical documents including news reports, medical literature and related analysis, we examine four instances of past scientific inquiry that demonstrate efforts to expand the community of peers to achieve both intrinsic and instrumental values. The parallels between these examples and contemporary engagement can inform current efforts.

Our assessment follows from two definitions. A stakeholder is an individual or organization with responsibility for or affected by health- or healthcare-related decisions [1]. This can involve a diverse range of groups, including but not limited to patients, citizens, providers, researchers, purchasers, payers, policy-makers, government agencies and nongovernmental organizations. Engagement is involvement in

research activities (including defining research topics, partnering in research and using research evidence) [18].

HIV/AIDS: patients' AIDS Coalition to Unleash Power

In the first year of HIV/AIDS, individuals with HIV faced devastating illness and high mortality rates. AIDS-related deaths skyrocketed, from 31 in 1981 to 18,447 in 1990. Frustrated by the perceived inaction of policy-makers and industry, people living with HIV founded the AIDS Coalition to Unleash Power (ACT UP) in 1987 to advocate for change.

The efforts of ACT UP's Treatment and Data Committee were especially far reaching. Driven by a commitment to engage diverse stakeholders through 'direct action to end the AIDS crisis', the committee sought to accelerate research that could improve clinical interventions. To achieve these changes, activists acquired a deep knowledge of medicine to enable their full participation in the research process [19].

This patient-initiated action "changed the very nature of patient advocacy" [20] – and did so with dramatic results. ACT UP engaged with the NIH to change funding priorities, with the US FDA to secure a fast-track policy for promising drugs, with the Centers for Disease Control & Prevention to redefine AIDS to reflect its impact on women and injection drug users, and with the pharmaceutical company Burroughs Wellcome to lower the price of azidothymidine, the first drug with potential to slow the progression of HIV [19,21]. These efforts became part of a success story for millions of people in the USA and across the globe [21].

Breast cancer: patients & clinicians advocate

As ACT UP was engaging on HIV/AIDS, a new treatment was gaining attention as a promising therapy for advanced breast cancer. High-dose chemotherapy plus autologous bone marrow transplant (HDC-ABMT) involved a two-pronged approach, coupling high doses of chemotherapy with infusion of bone marrow or stem cells.

Decision-making about coverage and access proved highly controversial. As a combination of previously approved therapies, HDC-ABMT was not subject to FDA approval [22]. Insurers initially resisted coverage, citing inadequate evidence. Patients, backed by well-organized advocacy groups and prominent oncology researchers, rapidly mobilized to demand access, successfully lobbying several states to mandate coverage and suing insurers that denied it [22]. This litigation resulted in several large verdicts for the plaintiffs and many insurers offered coverage to avoid further litigation [22].

Unfortunately, this advocacy also stymied clinical research. With insurance coverage, patients no longer

needed to enroll in clinical trials to receive HDC-ABMT. Ultimately nine in ten patients eligible for HDC-ABMT elected to receive it outside of clinical trials [22], dramatically decreasing the evidence base for treatment efficacy, and delaying the eventual finding of comparable results to standard-dose therapy [23]. The costs of this misadventure were staggering; an estimated 42,680 patients were subjected to unnecessary treatment and associated risks, at a cost of US\$80,000 per case and a total bill exceeding US \$3.4 billion [22].

Mammography: patients & clinicians resist

Mammography screening guidelines are issued periodically by the United States Preventive Services Task Force (USPSTF), an independent panel that develops recommendations for preventive health services. USPSTF is comprised of 16 recognized experts in prevention, evidence-based medicine and primary care. To develop recommendations, the panel engages partner organizations including major medical societies, insurers and patients in topic identification and question refinement before initiating guideline development, and in dissemination and implementation after guidelines are completed. However, it excludes patients and technical experts during guideline development, citing the importance of methodological expertise and minimizing potential conflicts of interests. Although USPSTF recommendations carry no official status, they are tremendously influential for clinical standards that guide care delivery and coverage decisions.

In 2009, the USPSTF issued revised breast cancer screening guidelines, advising against ‘routine’ mammography for women aged 40–49 years, and recommending that all women talk with their doctors about screening [24]. According to a former USPSTF member, these revisions were intended to convey a ‘nuanced point’ that screening decisions should include patient–clinician discussion, rather than to declare a radical departure from past guidelines [25].

The revised guidelines, however, unleashed vehement opposition. Radiologists, oncologists and patient advocacy groups claimed they “turn(ed) back the clock on the war on breast cancer” [26]. Others argued that the revisions created more confusion than clarification, and undermined trust in USPSTF recommendations [27]. Ultimately, many physicians and institutions resisted the revisions, reducing their impact on screening practices [28,29].

Vaccination: parents hesitate

In 1998, a (subsequently retracted) paper in *The Lancet* suggested that the measles, mumps and rubella vaccine could cause autism [30,31]. By 2004, measles vaccination

rates in Britain had plummeted to 80% – well below the 95% level the WHO recommends to ensure herd immunity [32]. Public concern about vaccine safety has persisted in the UK and elsewhere, and an increasing minority of US parents currently diverge from national vaccination guidelines [33–35]. Prior to recent state policy changes, vaccine refusals approached 70% in some wealthy Los Angeles (CA, USA) neighborhoods, on par with south Sudan [36]. Such refusals have led to a resurgence of vaccine-preventable illnesses including measles, pertussis and pneumococcal infections [37–39].

Vaccination refusal rates and apparent dissatisfaction among parents with recommended guidelines have led to calls for research on vaccine ‘hesitancy,’ [40] including research that engages parents to better understand the reasons for refusals [41].

Insights for current practice

These historical examples suggest several key insights for contemporary stakeholder-engaged research. They illustrate that the intended outcomes of engagement – why we do it – can influence the design of engagement activities. They also illustrate that the activities of engagement – who initiates it; who is involved; and how it is carried out – can affect outcomes. And finally, they show that external circumstances can shape engagement, often in unpredictable ways.

Consider & articulate all goals of engagement

Specifying engagement’s purpose can clarify priorities, while potentially revealing key tradeoffs. ACT UP sought democratic engagement through participation in research and healthcare to influence research outcomes. These were arenas in which its members, as socially marginalized patients, had typically been excluded. ACT UP’s founders valued drug safety and science-driven research because their very survival depended on it. The explicit declaration of these twin aims reinforced members’ commitment to engagement and it may have improved the organization’s capacity to make successful tradeoffs between instrumental and intrinsic aims of their work.

The USPSTF’s processes for mammography screening were designed to maximize the instrumental value of a scientifically valid guideline development process. Although these processes minimized conflicts of interest in guideline development, they ignored the potential instrumental and intrinsic values derived from full stakeholder participation. Fuller appreciation of the interplay between the instrumental and intrinsic values of stakeholder engagement might have enabled the task force to design a process that could have anticipated contentious issues before public release of the guidelines, and allowed them to

consider strategies for minimizing opposition and securing broader buy-in.

Effective engagement was absent from the HDC-ABMT breast cancer treatment case. Patient preferences for access to new therapies conflicted with the public health and clinical communities' long-term goal of ensuring safe and effective treatment, and no process was in place to address this tension. Patient-initiated advocacy proceeded independently of scientific inquiry and deep cleavages between investigators and clinical practice were the result.

Finally, childhood vaccination policy has historically pitted parental preferences against public health goals. Stakeholder engagement in vaccine research – specifically, engagement of parents – may expose an inherent tension between intrinsic values of autonomy in decision-making and instrumental values of optimizing population health. Although public health officials may seek engagement of vaccine-hesitant parents in the hopes of changing their attitudes about vaccination, parents may perceive engagement as a means to change vaccine policies they disagree with. Failing to acknowledge this tension may open the door to challenges of tokenism; should parents feel their views are not given fair weight. Clearly articulating the goals of engagement may support buy-in – and minimize the risk of undermining the trust necessary for current and future engagement activities.

Define the relevant actors

Who is engaged is critical to achieving desired outcomes. ACT UP's inclusive approach targeted a broad spectrum of relevant decision-makers. The resulting process improved therapeutic outcomes while including patients in decision-making from which they were historically excluded. In contrast, USPSTF's guideline development excluded selected stakeholders from key processes during the research cycle. Although excluding specialists and industry may serve valid, instrumental goals, exclusion in this case may have backfired. Specifically, exclusion diminished opportunities to anticipate pushback by affected groups, and may have undermined trust among patients, clinicians and the broader public.

Who initiates engagement also shapes its outcomes. ACT UP and HDC-ABMT were largely patient initiated, driven by reasonable frustration at being excluded from processes with deep and far-reaching implications for their own lives. However, contemporary engagement, such as that for vaccines, is often initiated by funders and researchers. Ideally, this may promote trust and buy-in, if researchers are viewed as being fair and neutral. Engaging parents in research and policy formulation has been suggested as a possible means to

improve adherence to vaccination guidelines, because it can increase researchers' and policy-makers' understanding of parents' concerns, and might enhance parents' confidence in the recommendations [41]. Although such an approach to engagement may offer instrumental value – an opportunity to anticipate concerns from affected stakeholders, and to incorporate stakeholder values and preferences into research and resultant policy decisions – it remains to be seen whether these potential benefits will, in fact, be realized.

Pay attention to process

How stakeholders are engaged affects outcomes. ACT UP's commitment to acquiring an understanding of virology, immunology, and regulatory affairs enabled them to work collaboratively with scientists and policy experts to achieve shared aims, accelerating development of effective treatments.

In the case of HDC-ABMT, there was no obvious mechanism to facilitate dialogue between advocates for expanded access to the breast cancer treatment and the researchers and policy-makers seeking further evidence. Consequently, decision-making was thrust upon legislatures and the courts, both of which proved deficient institutional mechanisms for structuring effective engagement. Ultimately, political pressure overwhelmed scientific evidence [22]. The lack of a forum for engagement obscured an opportunity for reconciliation of views.

Be aware that external circumstances may undermine outcomes

Under ideal circumstances, engagement demonstrates respect for stakeholders, identifies relevant research questions and yields research results that are incorporated into policy and practice – ultimately resulting in improved outcomes. Yet engagement cannot guarantee these results; researchers may find their goals overwhelmed by circumstances originating outside of the research environment. For example, while research suggests that engaging parents may increase their likelihood to support and comply with recommended vaccination guidelines [35], the broader public debate over vaccines has engendered deep divisions, leaving some parents distrustful of expert guidance, and some clinicians and public health officials derisive toward vaccine-hesitant parents. These background circumstances may constrain contemporary engagement efforts surrounding vaccination regardless of intent or design.

Conclusion

This paper revisits historical examples of stakeholder engagement to improve understanding of contempo-

rary challenges in engaging stakeholders in research. Although there has been considerable interest in stakeholder engagement, there has often been inadequate attention to the goals of engagement – and how they may conflict. Our analysis underscores the importance of developing clarity on the purpose of engagement activities, and the potential tradeoffs involved in engaging stakeholders in research. Defining what we want engagement to achieve – and communicating these goals transparently – can enable engagement activities to be designed so as to support its goals, to enable evaluation of efforts and inform improvement, and to maintain stakeholder trust. This paper offers several lessons for researchers to consider when defining the goals of an engagement activity, and in matching the design of engagement processes with those goals.

Future perspective

Though called by different names over the years, stakeholder engagement is not a new concept. Both history and theory support the promise of genuine benefits from engaging stakeholders in research. However, as the vaccine experience suggests, pay-off from engagement is not guaranteed. Moving forward, it is worth exploring whether persistent engagement with the world beyond the research environment might help researchers manage external obstacles, understand stakeholders' competing

values, and flag potential trouble spots before they undermine research.

History also suggests that researchers may need to assist stakeholders to become fully prepared to participate; this is especially important for enabling genuine involvement in multistakeholder settings. Further research is needed to determine ways to educate lay persons, including citizens and patients, to support their ability to participate meaningfully in research. Moreover, additional investigation is warranted into how the setting impacts stakeholders' ability to meaningfully communicate and consider relevant views.

Finally, and most importantly, clear articulation of goals – both at the level of individual studies, and at the level of broader policies – will improve our chances of fully understanding the short- and long-term effects of current efforts, and guide researchers in achieving intended outcomes. Understanding the purpose of stakeholder engagement in research – and implications for whom and how to engage – is critical to the success of contemporary engagement activities, and is required for a genuine commitment to this endeavor. As these historical examples demonstrate, failure to explicitly consider the purpose of engagement – and its potential tradeoffs – may undermine the ability of engagement to yield desired benefits. The current focus on stakeholder engagement offers an opportunity to set criteria for success, and to assess achievement in avoiding past mistakes.

Executive summary

Background

- Insufficient attention has been directed at the ends of engagement: what do we intend engagement to achieve and how do we know if engagement has achieved the intended ends?
- Clearly articulating the goals of engagement within each research activity will provide a framework to evaluate success and inform improvement.

Historical case studies

- Historical perspective methodology can support understanding of current events through analysis of similar historical cases, integrating past events to inform current contexts. We analyze four instances of previous engagement in research to inform current efforts.

Insights for current practice

- Consider and articulate all goals of engagement – specifying engagement's purpose can clarify priorities, while potentially revealing key tradeoffs.
- Define the relevant actors – who is engaged and who initiates engagement will shape the outcomes of engagement activities. Excluding relevant stakeholders may create backlash that undermines research goals.
- Pay attention to process – how stakeholders are engaged influences the outcomes of engagement. Training of lay stakeholders in the science and methodologies of research can enhance capacity for meaningful engagement.
- Be aware that external circumstances may undermine outcomes – activities originating outside the research environment may influence contemporary engagement efforts.

Conclusion

- Stakeholder engagement is not a new concept. Historical experiences can inform contemporary efforts.
- Although both theory and process support the promise of genuine benefits from engaging stakeholders in research, the payoff is not guaranteed.
- Understanding – and clearly articulating – the goals of engagement is critical to the success of contemporary engagement.

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employ-

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