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**Author:** Peay, Holly Landrum

**Title:** Community-engaged approaches to explore research priorities in Duchenne and Becker muscular dystrophy

**Issue Date:** 2015-04-21



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Setting an advocacy  
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# Introduction

## CHAPTER 1.

### Setting an advocacy agenda using community-engaged research in Duchenne/Becker muscular dystrophy

#### Community Engagement

Community engagement is a form of public participation that is defined as “the process of working collaboratively with groups of people affiliated by geographic proximity, special interests, or similar situations with respect to issues affecting their wellbeing.”<sup>1</sup> It is an approach, rather than a specific method, which values and fosters collaborations among the individuals who are the focus of the program, initiative or study; the group(s) implementing the program; and others with influence such as community leaders and government agencies. Approaches can vary dramatically in the degree of community engagement, from passive involvement through information dissemination to the target community, to active partnership of community stakeholders as decision making members of the program leadership team.<sup>2</sup>

Underlying community engagement approaches is the concept of **empowerment through participation**. In this context, participation has been described as: “...the process that increases a community’s capacity to identify and solve problems.”<sup>3</sup> Meaningful community participation includes the generation of ideas, contributions to decision making, and a shared responsibility for the program or intervention.<sup>4</sup> The approach is grounded in principles of fairness, justice, and self-determination.<sup>4</sup> In recent decades, public participation has evolved from an adversarial approach characterized by resistance to the establishment to active solicitation of stakeholder input by public authority figures.<sup>5</sup>

#### Community-Engaged Research

Community-engaged research (CEnR) is a collaborative research approach where researchers engage stakeholders to propose and answer questions of interest and relevance to the stakeholder community. In this thesis, we integrated the perspectives and preferences of a broad range of stakeholders into the research process, including patients, caregivers, clinicians, patient advocates, clinical researchers, and clinical trial sponsors. CEnR is often used as a

catalyst for changing policies, programs, and practices.<sup>1</sup> It presupposes that people affected by the research have a right to influence what research is done and how it is conducted,<sup>6</sup> and that "...health issues are best addressed by engaging community partners who can bring their own perspectives and understanding of community life and health issues to a project."<sup>4</sup> The increased relevance that comes from community engagement is expected to improve the uptake of the evidence and the likelihood that patients will achieve the health outcomes that are important to them.<sup>7</sup>

Without community engagement, researchers risk imposing their own concepts of the most important health or policy concerns on a disease community. This could result in research that is less relevant to the community that channels resources away from the most important challenges.<sup>8</sup> Even clinicians expert in managing the health care needs of a patient population are oriented toward inquiry about health or healthcare, rather than the lived experience of the patient.<sup>7</sup>

A challenge of public engagement is that the approach is poorly conceptualized, spanning theoretical principles to nuanced, measurable engagement efforts.<sup>5</sup> To improve conceptualization, five core principles of CEnR were identified: understanding the definition and scope of community engagement in the research process; developing strong partnerships between communities and researchers that include mutual understanding of needs, capacities, and goals; facilitating equity of power, expertise, and responsibility while encouraging diverse perspectives; building capacity in all partners; and effective information dissemination based on bi-directional, transparent communication and mutual decision making about results dissemination.<sup>9</sup> Similarly, dimensions of community participation in biosciences include participant education, empowerment in goal setting, control over resources, the capacity to exit without penalty, opportunities to influence outcomes, measurement of outcomes, and within-group communicative capacity.<sup>5</sup> Strong partnerships help community members feel ownership over the program outcomes and to empower them to become agents for change.<sup>3</sup> An important caveat is that CEnR must not reduce scientific rigor.<sup>7</sup>

A review of community engagement in research partnerships identified areas in which community engagement has made a positive impact.<sup>6</sup> These include: influencing the research agenda; improving study design, research tools and outcome measures; and improving recruitment.<sup>6</sup> A second systematic review of patient and public involvement in

research found that researchers developed respect for and rapport with the community and greater insight into their areas of research.<sup>10</sup> There were both positive and negative impacts on the community involved in the research—increased knowledge and awareness about their condition, but also perceptions of insufficient training to contribute to research and a sense of being overburdened.<sup>10</sup>

Community-engaged research is most often described in the context of major public health issues and/or research in traditionally underserved communities.<sup>6</sup> In this thesis community engagement is employed in a different context: a rare, progressive, fatal disorder with high unmet needs (described further below). Use of community engagement is compelling in this community because there are many competing needs and limited resources. Arguably the most impactful research would be done after engaging with the community and identifying the most feasible and pressing research needs.<sup>7</sup> The research was intended to be translational in that it would directly inform the planning of an advocacy agenda.

To better characterize the public engagement used in this thesis, we present a model that describes a continuum of approaches to community-engaged research. The model is adapted from the United States-based ACQUIRE group's Active Community Engagement (ACE) Continuum;<sup>2</sup> the adaptations were based on the literature<sup>1-9</sup> and our experience. The model describes "stakeholder" engagement. Depending on the research objectives, stakeholders in disease communities may extend beyond patients and caregivers to also include clinicians, clinician researchers, industry groups, and advocacy organizations. The model is revisited in the concluding chapter to explore the depth and breadth of engagement in this thesis and to assess the CEnR approaches employed.

**Table 1. Community-Engaged Research Continuum (adapted from Russell et al., 2008)**

<b>Characteristics of community engagement</b>	<b>Level 1</b>	<b>Level 2</b>	<b>Level 3</b>
<b>A. Inclusion of stakeholders in research program development</b>	<ul style="list-style-type: none"> <li>Aims and methods developed by professionals with expertise in the disease/community (i.e., specialist clinician or educator), and/or using public resources such as social media</li> <li>Aims/methods reviewed by and instruments informed by members of target population</li> </ul>	<ul style="list-style-type: none"> <li>Aims and methods are researcher developed and modified based on input from one or small number of patients/caregivers</li> <li>Members of target population have moderate input into instrument choice or development</li> </ul>	<ul style="list-style-type: none"> <li>Committee of stakeholders including patients/caregivers collaborate with research team to develop study aims and methods</li> <li>Members of target population have significant input into instrument choice or development</li> </ul>
<b>B. Inclusion of stakeholders in decision making</b>	<ul style="list-style-type: none"> <li>One time, short-term input solicited from influential community leaders before or during study</li> </ul>	<ul style="list-style-type: none"> <li>Community leaders and/or patient representatives advise research team at pre-identified time points before or during study</li> </ul>	<ul style="list-style-type: none"> <li>Leadership committee comprising multiple stakeholders integrated as part of study team</li> </ul>
<b>C. Increasing stakeholders' research advisory capacity</b>	<ul style="list-style-type: none"> <li>Researchers provide general education to patient community about area of research</li> </ul>	PLUS <ul style="list-style-type: none"> <li>Provide specific information and/or training to stakeholders who advise the research team</li> </ul>	PLUS <ul style="list-style-type: none"> <li>Develop a collaborative research leadership team where each members' expertise is equally valued and all learn together</li> </ul>
<b>D. Disseminating study information</b>	<ul style="list-style-type: none"> <li>Patient-oriented recruitment materials describing aims, inclusion and exclusion criteria distributed through community forums</li> <li>Study results available in professional version</li> </ul>	PLUS <ul style="list-style-type: none"> <li>Introductory study information provided in lay terms, independent of recruitment efforts</li> <li>Study updates in lay language</li> <li>Lay summary of results actively disseminated to the community</li> </ul>	PLUS <ul style="list-style-type: none"> <li>Patients/caregivers actively involved in planning the information dissemination</li> <li>Patients/caregivers involved in developing meaningful, understandable lay summaries</li> </ul>
<b>E. Developing accountable policy, service, and/or intervention recommendations based on outcomes of research program</b>	<ul style="list-style-type: none"> <li>Recommendations are determined by professionals with expertise in the disorder/community</li> </ul>	<ul style="list-style-type: none"> <li>Recommendations are developed by research team and modified based on input from one or a small number of patients/caregivers</li> </ul>	<ul style="list-style-type: none"> <li>Consensus recommendations are determined after community engagement; and/or through input of collaborative research leadership team</li> </ul>

## Duchenne and Becker Muscular Dystrophy

Duchenne and Becker muscular dystrophy (DBMD) are rare X-linked neuromuscular disorders that occur primarily in males. The progressive muscle wasting that is the hallmark of the conditions is caused by mutations that alter production of the dystrophin protein.<sup>11</sup> Of the two conditions, Duchenne muscular dystrophy (DMD) is more severe and more common, with an incidence between 1:3500 and 1:6200.<sup>12</sup> Symptoms may appear as early as infancy and diagnosis usually occurs around age 5.<sup>13,14</sup> The phenotype includes progressive muscle weakness and death occurs typically in the late 20s.<sup>13</sup> Becker muscular dystrophy (BMD) is about a third as frequent and is more heterogeneous, ranging from a course similar to Duchenne to much milder presentations with later onset.<sup>12</sup> Several studies have shown high caregiving demand, burden, and stress,<sup>15-19</sup> and lower psychosocial and health-related quality of life<sup>20-21</sup> in caregivers of children with DBMD. Managing Duchenne places serious financial burden on the family.<sup>22</sup>

The first multi-system care guidelines for DBMD were published in 2009.<sup>23</sup> The standard-of-care treatment for DBMD includes the off-label use of corticosteroids, which stabilize muscle strength, delay loss of ambulation, and improve cardiopulmonary function.<sup>23-24</sup> There are no U.S. Food and Drug Administration (FDA) approved treatments for DBMD. In 2014 the European Medicines Agency (EMA) granted conditional approval for a drug that targets approximately 13% of patients with Duchenne.<sup>25</sup> Several other potential therapies are under clinical trial<sup>26</sup> or have recently completed clinical trials.<sup>27</sup> These potential treatments represent a new opportunity to intervene in a fatal disorder.

The DBMD field is at a time of tremendous advancement with robust pre-clinical research and a wide range of targets that span numerous primary and secondary pathways (for examples and a lay summary,

see [http://www.parentprojectmd.org/site/PageServer?pagename=Advance\\_pipeline](http://www.parentprojectmd.org/site/PageServer?pagename=Advance_pipeline)). These advancements have led to increased optimism among families, clinicians, and the advocacy community. However, most patients do not have access to novel, potentially disease-modifying therapies because participation in clinical trial is not available to them. The large majority of families have thus seen only modest changes in the management of their children with DBMD—though it is important to note that those improvements in care have led to advances in lifespan.<sup>12,24</sup> Families with access to clinical trials have to make difficult decisions about whether to enroll their child in a clinical trial, and if so, which trial to choose. Given the considerable



needs imposed by both the disorder and this time of growth in knowledge and opportunities, DBMD provides an appealing model for conducting community engagement to help ensure that research is focused on timely and pressing needs.

### **Aims and Community-Engaged Approaches of the Thesis Studies**

The research studies included in this thesis were developed to inform the priorities and agenda of a DBMD advocacy organization called Parent Project Muscular Dystrophy (PPMD). The studies represent a range of research aims, methodologies, and levels of community engagement. Prior to each study, community engagement identified areas of need; the four distinct areas of significant need are introduced below and described in each subsequent chapter of the thesis.

#### ***Informing interventions for mother caregivers using a stakeholder advisor approach: The Mothers' Wellbeing Study (Chapter 2)***

The impetus for the first study came from years of anecdotal reports to the advocacy organization about mothers' unmet caregiving and support needs. A small body of published literature confirms the impact of caring for children with Duchenne or Becker muscular dystrophy on caregivers. However, mothers' anecdotal communications highlighted important gaps in the literature—as well as a gap in understanding and addressing their needs, they spoke to understanding areas of strength and benefits conferred by the caregiving experience, and undertaking efforts to enhance their adaptation to caregiving for a child with DBMD.

Therefore, the goal of the study was to inform PPMD's ongoing and future efforts to improve wellbeing in mothers of individuals with DBMD. Chapter 2 presents cross-sectional data on mothers' unmet support needs and longitudinal data from the same sample on predictors of Duchenne-specific adaptation. In this CEnR approach we involved key stakeholders as advisors in the development of the longitudinal survey study. These advisors guided study objectives, aims, and methods, and helped maintain a focus on obtaining results that might lead to meaningful interventions. Advisors and parent pilot testers reviewed validated measures and informed the development of novel items on mothers' needs and strengths. The advisors and PPMD staff also recommended plans for dissemination of study findings.

***Influencing regulatory decision making using a collaborative, community-led approach: Duchenne Treatment Preferences Study (Chapters 3-5)***

The second study was developed to answer specific policy-related questions of immediate relevance to the DBMD population. As clinical trials in DBMD have progressed, questions emerged from trial sponsors and regulators about parents' and patients' treatment preference and risk tolerance. Historically, most patient and caregiver feedback is provided to regulators through testimonials. This approach has many limitations; the most significant is that those who provide testimonials may not represent the views of the entire patient population.<sup>28,29</sup> Thus, regulators are being asked to incorporate additional patient and caregiver input to include the views of larger groups of stakeholders,<sup>30</sup> and draft FDA Guidance indicated a willingness to include quantification of treatment preferences and risk tolerance in the regulatory process.<sup>31</sup> An overarching objective of the program was to develop a replicable model for advocacy directed at informing regulators' benefit-risk assessments.

This research program was intended to engage parents of individuals with DMD about both the DMD disease impact and their treatment preferences and risk tolerance. Three manuscripts have emerged from this study and are included in this thesis. We explored one aspect of disease impact, parental DMD-related worries, by using Best-Worst Scaling (BWS) Case 1 (Chapter 5). BWS Case 1 is used to assess participants' relative preferences for a series of related items that could otherwise be evaluated using a rating or ranking scale.<sup>32</sup> However, advantages of BSW Case 1 to rating scales have been demonstrated.<sup>32</sup> During the worries tasks, parent participants were presented with 16 sequential sets of worry items. For each task participants identified the items that were most and least worrying over the past 7 days.

The treatment preferences task described in chapters 3 and 4 used a more complex form of BWS, called BWS Case 2, as well as simple conjoint analysis. Both BWS Case 2 and conjoint analysis involve participants stating their preferences about treatment profiles that are presented to them.<sup>32</sup> The treatment profiles typically include different levels of treatment benefit and levels of risks, harms and/or burden. For the BWS Case 2 tasks, participants were presented with 18 simulated treatment profiles and asked to identify the best and worst aspects of each. Every treatment profile was followed by a simple conjoint task where participants indicated acceptance or rejection of the treatment, if it were available. The article under Chapter

3 reports the results of the BWS case 2 analysis, while Chapter 4 describes a comparison of the BWS and conjoint approaches.

The development and implementation of this study included rounds of community education about the objectives of the study and the study implications. It was led by PPMD with considerable organization investment. The process included extensive reporting back to stakeholders and was described and received as a community project. Study decision making rested with a small study team comprising the researchers, the President of PPMD, and several other advocacy organization staff members and volunteers with a range of backgrounds. Stakeholder advisors including families, clinician investigators, and industry professionals, all of whom had extensive input into the development of the items in the treatment preferences task. Items for the Duchenne worries task were developed by five parent volunteers.

***Informing clinical trial processes and informed consent procedures using a community-based participatory research approach: Clinical Trial Expectation and Decision Making Studies (Chapters 6-8)***

The third thesis topic assesses the implications of a relatively new phenomenon in DBMD—access to clinical trials. The research under this topic included two separate studies that explored the experiences and perceptions of parents whose children were enrolled in Duchenne clinical trials. The first was a pilot study to understand positive and negative outcomes of one trial sponsor's community engagement in trial development. An article describing that study is included as Chapter 6. The second was a community-based participatory research study with a focus on trial decision making in a range of DMD clinical trials. Two manuscripts from the second study are included as Chapters 7 and 8.

The pilot study was initiated with the support of PPMD and the qualitative interview themes were developed with their input, with an expectation that results would be used to influence community engagement for future clinical trials. Unexpectedly, the clinical trial failed immediately before the study was submitted for IRB review. Thus, the focus of the study shifted to parents' expectations of the trial and response to the trial failure.

The findings from the pilot study (Chapter 6) emphasized the need to extend our conceptualization and assessment of influences on clinical trial decision making and decision

making processes. Our intention to improve and nuance existing notions of therapeutic misconception, optimism, and mis-estimation (collectively called “therapeutic error”<sup>33</sup>) led to a project on parents’ expectations, hopes, and clinical trial experiences in a broad range of DMD trials. The project used a community-based participatory research (CBPR) approach, in which advocates, clinicians, caregivers, and social science researchers identified the research agenda, design and delivery and led the research program.<sup>4,5</sup> The CBPR study included a qualitative phase and a subsequent survey phase (the latter is not described here). The interview study explored perceptions of parent decision makers as well as clinician investigators at trial sites. Results were intended to inform a conceptual decision making framework, recommendations to trial sponsors and advocacy organizations, and the development of a subsequent survey. Chapter 7 reports on parents’ perceived benefits of trial participation, and Chapter 8 integrates study results and the CBPR team’s guiding principles to support a decision making framework for clinical trial participation.

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