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

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Discussion, Summary and Implications

Conclusions

CHAPTER 9.
Summary, Discussion and Implications

This thesis presents a series of translational research studies. They employ a diverse set of research methods to explore topics of importance to a patient community. In this section we summarize the outcomes and implications of each study, after which the community-engaged research (CEnR) approaches employed in the studies are rated and reviewed.

A common limitation shared by all of the studies was the use of PPMD and the DuchenneConnect self-report registry for recruitment. Families who opt into participating in a disease advocacy organization or a self-report registry, and who then opt to participate in a social science study, may not be representative of families managing Duchenne and Becker muscular dystrophies. Future research would benefit from additional consecutive in-clinic recruitment to improve the range of perspectives that are included in qualitative research and to ensure generalizable quantitative research.

Advocacy and programmatic implications

The overarching objective of the studies was to inform PPMD's interventions and/or policy and advocacy approaches. Though the impact varied, all were successful in that objective. Achieving the objective was facilitated through the use of a range of community engagement approaches.

Mothers' wellbeing studies (Chapter 2) provided clinically-relevant data about mothers' unmet support needs and adaptation to caregiving for a child with DBMD. The pragmatic and positive focus of the study aims and instruments reflected stakeholders' attitudes that caring for a child with DBMD comes with benefits, and clinical interventions should highlight strengths and wellbeing rather than burden and deficit.

Mothers identified many areas of resilience and support. We identified a need to improve use of respite care. Findings also showed that the least-met support needs are related to coping with challenging emotions associated with DBMD. Predictors of psychological adaptation included greater resilience and endorsement of positive impact of DBMD on the family. Though existing literature places emphasis on burden of illness, we found that perceived burden did not predict adaptation.

Study results include unexpected findings about mother's age, child's disease progression, psychosocial support needs, and adaptation. We found opposite effects of mother's age (with younger age predictive of higher adaptation scores) and child's functional status (with worse functional status associated with, but not an independent predictor of, higher adaptation scores) on mothers' psychological adaptation. The results suggest that while mothers may be able to attribute more benefit to the DBMD experience and perceive lower unmet needs as their children's symptoms become more advanced, their resilience may be challenged as they age. Additional exploration is needed to better understand the effects of increasing mother's age and worsening child's functional status on psychosocial needs, care facilitators, and psychological adaptation.

Clinical implications from the study on mothers' wellbeing include the need for systematic exploration of caregivers' unmet support needs, especially those related to coping with DMD-related uncertainty and fear. Efforts to improve mothers' adaptation should focus on fostering resilience and enhancing benefit finding through identification of positive aspects of living with DBDM. Clinicians may be able to identify specific caregiving needs and customize interventions based on the use of simple, targeted questions similar to the questions used in this study.

Summaries of the research findings have been shared through Parent Project Muscular Dystrophy forums, including social media and the PPMD annual conference. Data presented in this thesis informed a wellness intervention at PPMD's annual conference in 2013 and was used to support two grant proposals on caregivers' wellbeing. In late 2014 we initiated a carrier mothers' program guided by the study results through DuchenneConnect, a longitudinal patient and caregiver self-report registry. In addition, the longitudinal mothers' wellbeing study is ongoing. To extend the results from the first two years of data collection, the third year's survey included measures on uncertainty, spirituality, and hope.

In the **treatment preferences and impact study** (Chapters 3-5), using Best-Worst Scaling methodology we found that caregivers were willing to accept increased risk for a serious or fatal outcome when balanced with a non-curative treatment, even absent lifespan improvement. The addition of a simple conjoint analysis as a second stated preferences method validated the major findings and provided important, policy-relevant information about intention to use specific therapies. In the worry study we successfully differentiated among a set of highly relevant

worries, concluding that the most pressing concerns entailed worries about symptom progression and access to medical care, followed by the child being happy. Worries related to parents' wellbeing and family and social impact were relatively less prioritized. Best-Worst Scaling represents a compelling method to explore and quantify disease perceptions and impact that is rarely used in health-related social science studies.

Of the studies presented in this thesis, the treatment preferences study had the most remarkable advocacy and policy impact. We described a model process for advocacy organizations aiming to promote patient-centered drug development. Study results were distributed to the U.S. Food and Drug Administration (FDA) personnel at several in-person forums to inform their assessment of emerging DMD therapies. The study has been cited by FDA personnel, who identified it as a replicable template for other advocacy organizations to follow[1] and stressed the need for such research to be conducted by other organizations.[2] Several biopharmaceutical companies have used or plan to use the data from this study in their regulatory processes. The study was also cited in the U.S. House of Representatives Energy and Commerce Committee 21st Century Cures Initiative and described in a Committee hearing.[3]

The study results provided PPMD with a compelling message for FDA engagement. This led the FDA to urge PPMD to develop draft guidance for DMD—a first for a rare-disease advocacy group. It was submitted to the FDA on June 2014. The guidance begins with a chapter on benefit/risk assessment, which includes a summary of the results and advises sponsors to measure patient/caregiver preferences as part of their drug development and regulatory submission processes.[4]

Since completing the study, the authors have presented the results at more than 20 professional and advocacy venues. Almost a dozen advocacy organizations in other disease areas have indicated their intent to use it as a model. As a representation of ongoing impact, in November 2014 PPMD announced a collaboration with Santhera Pharmaceuticals to develop a new benefit/risk study focused on pulmonary therapies for Duchenne.[5]

Decision making in clinical trials (Chapters 7-8) is an area of considerable interest for clinical trial sponsors, clinical trial site teams, institutional review boards, and advocacy organizations. Our studies highlighted the complexity of clinical trial decision making, especially in the context

of a rare, progressive pediatric disorder, where our parent participants equated doing “nothing” (i.e., not participating in a trial) with doing harm. Parents’ decisions were strongly influenced by the chance for individual benefit to their children, but the participants did not display classically-defined therapeutic misconception. The adaptive optimism engendered by the availability of trial participation was another anticipated benefit—and one that was highly valued by both parents and clinicians on clinical trial teams. Parents reported undertaking a benefit-risk assessment and developing intentions to participate in clinical trials before the informed consent process.

Clinicians described more influence on parental decisions than attributed by parents. They reported feeling responsible to facilitate informed decisions while maintaining parents’ optimism. Based on the findings we suggest that clinicians, sponsors, and advocacy organizations develop approaches to engage families in anticipatory guidance about potential negative trial outcomes, anticipating that these efforts may assist clinicians in having balanced discussions with families while providing some protection against decisional regret.

We also provide a report of how parents assessed and valued perceived benefits during clinical trial participation, which has implications for their continued investment in the trial. Participants described a complex, dynamic process of defining, evaluating, and assessing “net benefit” as an ongoing coping process. Most perceived individual benefits to their children, as well as other benefits that included altruism, close relationships with the research team, and enhanced optimism.

Results from both interview studies informed the development of a quantitative survey about clinical trial decision making, for which recruitment has recently closed. To inform future research, we are in process of using the qualitative and quantitative results to adapt Leventhal’s common-sense model of self-regulation, which describes responses to and management of health threats[6]. The revised model will propose that decisions about disease management include expectations and hopes as cognitive and emotional appraisals that inform parallel cognitive and emotional processing. This will provide a framework to assess decision making influences and processes in the clinical trial context. We next plan to develop and evaluate a decision aid that focuses on identifying and distinguishing between clinical trial expectations and optimistic hopes.

Data from these studies have been presented to clinical trials sponsors in group and individual settings; to relevant organizations such as the Patient Centered Outcomes Research Institute and through the Clinical and Translational Science Award (CTSA) program; to clinician investigators at the World Muscle Society and other professional forums; and to patients and families through PPMD forums. The data have been used to inform the development of new educational content for patients and families and to justify sessions on trial expectations at the PPMD annual conference. Finally, themes from the study have been integrated into research exploring clinical trial decision making in other disease communities (spinal muscular atrophy, fragile X syndrome and HIV).

Implications for Community-Engaged Research Approaches

Table 2 presents a rating of the approaches used in this thesis on the CEnR continuum. We found that community engagement at level 1 or higher on the continuum is important to posing and answering questions of importance. The utility and feasibility of higher levels of community engagement varied based on the program's timeline, budget and needs. The community-based participatory research (CBPR) approach we used in the clinical trial study was extremely beneficial, but required a supporting timeline and budget that may not always be feasible. In the treatment preference study, the researchers and advisory team chose to target community engagement around communicating about the need for, and implications of, the study and for identifying the attributes and levels used in the instrument. We found that 'hybrid' community engagement approaches were natural for research conducted within an advocacy organization, and took advantage of PPMD's community reach and respect.

Table 2. Rating of Community-Engaged Research Approaches

Study	Mothers' Wellbeing Study	Duchenne Treatment Preferences	Clinical Trial Expectations Pilot	Clinical Trial Expectations and Experiences
A. Inclusion of stakeholders in research program development	Level 3	Level 2 (+ significant input, item development)	Level 1	Level 3
B. Inclusion of stakeholders in decision making	Level 2	Level 2	Level 1	Level 3
C. Increasing stakeholders' research advisory capacity	Level 2	Level 2	Level 1	Level 3
D. Disseminating study information	Level 3	Level 3	Level 1 (+ lay summary)	Level 3
E. Developing accountable policy, service & intervention recommendations	Level 2	Level 3	Level 2	Level 3

Lessons on Community Engagement

Following are some of the important lessons we learned about community engagement.

- In the mothers' welling study, our engagement efforts highlighted the importance of framing the disease experience. Findings underscore the need to re-orient negative predictor and outcome variables used in traditional disease impact studies to positive predictor and outcome variables that are focused on wellbeing.
- In the treatment preferences study, the importance of researcher flexibility when faced with stakeholders' responses to engagement efforts was recognized. Even with

engagement, not everyone in the community was in agreement about the value of providing quantified data to regulators. Thus, we added a complimentary approach (PPMD's "Share your Story" outreach, which resulted in an FDA-focused resource called "Patients are Waiting"[7]) to increase community acceptance and demonstrate our appreciation for the power of patient and family testimony.

- The clinical trials studies highlighted the benefits of a highly-engaged CBPR approach for addressing complex ethical issues with implications for a wide range of stakeholders. Incorporating a wide range of experienced stakeholders in the process helped to frame ethical challenges in an acceptable way and suggested future research and interventions that should be satisfactory to the community.

The community engagement undertaken in these studies had an important, and sometimes dramatic, impact on the study objectives, aims, design, analysis, interpretation, and dissemination. There is likely not a one-size-fits-all approach to community engagement. Instead, engagement must be done meaningfully so stakeholders have a real chance to understand and influence the research agenda. Long-term engagement requires education and support to expand parents' and caregivers' research imaginations, so they can be active participants in setting a research agenda. Researchers must be open to change and appreciate that their perspectives and research experiences will expand and grow as a benefit of the engagement.

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