



Using the MDIC Patient-Centered Benefit-Risk Framework to Support an Expanded Indication

A Case Study of the Science of Patient Input Program of the Medical Device Innovation Consortium (MDIC)

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SUMMARY

Home hemodialysis device manufacturer, NxStage, used the MDIC Patient-Centered Benefit-Risk (PCBR) Framework as a guide in developing a patient preference survey to quantify the acceptable risk of hemodialysis home alone versus at a dialysis center. Data from that survey were taken into consideration in FDA CDRH's decision to clear an expanded indication for NxStage's home hemodialysis device – the first 510(k) clearance in which quantitative patient preference data played a role.

THE PATIENT EXPERIENCE: DIALYSIS IN-CENTER VERSUS AT HOME

Hemodialysis is a type of dialysis in which blood is pumped from the body, through a filter, and back into the body. In-center treatment typically requires patients to travel three times per week to a dialysis center to receive dialysis for four hours at a time. *Source: [National Institutes of Health National Institute of Diabetes and Digestive and Kidney Diseases \(NIH NIDDK\)](#)*

Home hemodialysis (HHD), in which treatment takes place at the patient's home (or outside of a clinical setting), can be a more convenient option for some patients because they do not have to travel to the clinic, can dialyze on their own time, and are usually able to have more frequent treatments.

But, HHD also comes with several risks and responsibilities and requires that patients historically have been required to have a trained and qualified care partner present during treatments. *Sources: [NIH NIDDK](#), [Kidney Foundation](#)* Because HHD was only previously cleared by FDA for use with a care partner, patients who lived alone or lost access to a care partner were not eligible for HHD and could only receive dialysis in-center.

Home hemodialysis that is cleared for solo use (solo HHD) could increase treatment options for those dialysis patients who do not have care partners present and who are willing to accept the associated risks of solo treatment.

REGULATORY SCIENCE OPPORTUNITY

NxStage's HHD device received clearance for home hemodialysis in the presence of a care partner during waking hours (in 2005) and sleeping (nocturnal) hours (in 2014). The company sought an expanded indication for their device to be used by the patient alone during waking hours. (See **Box 1. Benefits, Risks, and References for the NxStage System One** (information provided by NxStage). *Read more from NxStage about [the risks associated with solo home hemodialysis.](#)*)

Box 1: Benefits, Risks, and References for the NxStage System One (information provided by NxStage)

More frequent hemodialysis using the NxStage System One is associated with a lower than expected risk of death when compared to conventional three times per week in-center hemodialysis^{i-v}, may help reverse a common type of heart damage called LVH (left ventricular hypertrophy)^{vi-ix}, and may help control blood pressure and reduce the need for blood pressure medications.^{vi,x}

Not everyone will experience the reported benefits of home and more frequent hemodialysis. HHD with the NxStage System requires a patient (and partner, if applicable) who are committed to being trained on and following the guidelines for proper system operation.

References:

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- ii. Miller BW, Collins AJ, Finkelstein FO, et al. Daily hemodialysis (DHD) is associated with lower than expected mortality. Abstract presented as poster at American Society of Nephrology Conference, October 29, 2009
- iii. Blagg CR, Kjellstrand CM, Ting GO, Young BA. Comparison of survival between short-daily hemodialysis and conventional hemodialysis using the standardized mortality ratio. *Hemodial Int.* 2006;10(4):371-374.
- iv. Kjellstrand CM, Buoncristiani U, Ting G, et al. Short daily haemodialysis: survival in 415 patients treated for 1006 patient-years. *Nephrol Dial Transplant.* 2008;23(10):3283-3289
- v. Woods JD, Port FK, Stannard D, Blagg CR, Held PJ. Comparison of mortality with home hemodialysis and center hemodialysis: a national study. *Kidney Int.* 1996;49(5):1464-1470.
- vi. FHN Trial Group. In-center hemodialysis six times per week versus three times per week. *N Engl J Med.* 2010;363(24):2287-2300.
- vii. Fagugli RM, Reboli G, Quintaliani G, et al. Short daily hemodialysis: blood pressure control and left ventricular mass reduction in hypertensive hemodialysis patients. *Am J Kidney Dis.* 2001;38(2):371-376.
- viii. Buoncristiani U, Fagugli R, Ciao G, et al. Left ventricular hypertrophy in daily dialysis. *Miner Electrolyte Metab.* 1999;25(1-2):90-94.
- ix. Ayus JC, Mizani MR, Achinger SG, et al. Effects of short daily versus conventional hemodialysis on left ventricular hypertrophy and inflammatory markers: a prospective, controlled study. *J Am Soc Nephrol.* 2005;16(9):2778-2388.
- x. Jaber BL, Collins AJ, Finkelstein FO, et al. Daily hemodialysis (DHD) reduces the need for antihypertensive medications. Abstract presented at American Society of Nephrology Conference, October 29, 2009.

Todd Snell, SVP of QA, Regulatory & Clinical Affairs at NxStage, said that seeking an expanded indication was often debated internally, but the decision to move forward was catalyzed by discussions with patients at a kidney disease workshop.



“In our case, we wanted the contraindication that HHD can’t be performed alone to be removed. It was not a risk that we could completely mitigate with technology, meaning we couldn’t add design features to eliminate the risks that are inherent to the therapy. But enough patients were vocal about wanting solo HHD and we thought that by not having that option we might be missing potential benefits of treatment for some patients,” he said. “It became a question of ‘does the benefit outweigh the risks?’ A clinical study would be difficult because only a patient could answer this question.”

APPROACH

The journey toward the patient preference study began with exploratory discussions at a 2015 Kidney Health Initiative (KHI) patient preference workshop. There, patients, regulators, and industry discussed the potential use of preference data to expand the labeling of existing HHD therapies to include patients without a care partner. As NxStage began to pursue the expanded indication, they intended to only conduct a qualitative survey (direct preference) to learn more about patients’ preferences. But they quickly realized through discussions with FDA that they needed more statistical rigor in their method for measuring risk and thus needed to conduct a quantitative patient preference study.

Familiar with the [FDA’s obesity patient preference study](#), but relatively new to the science of patient input, Todd and colleagues consulted the [MDIC Patient-Centered Benefit-Risk \(PCBR\) Framework](#) to better understand patient preference studies and to develop a patient survey to quantify the acceptable risk of hemodialysis home alone versus at a dialysis center.

“We referred to three separate sections of the MDIC PCBR Framework: the obesity study to understand what FDA studied in terms of preferences and how the study was done, the ‘factors to consider in undertaking a patient preference study’ section for planning, and the ‘methods review’ section, which was helped us speak the same language with those patients surveyed as well as FDA,” he said. (See **Box 2** for more detail on these sections of the MDIC PCBR Framework).

Box 2: MDIC PCBR Framework Content Used by NxStage in the Development of its Patient Preference Study

PCBR Framework Content	Location	Content Overview
CDRH-Sponsored Weight Loss Devices Study	End of Sections I-VI: p. 16, p.28, p. 38, p.47, p. 59, p. 72	Introduction to the CDRH study and illustration of key concepts using the CDRH study as an example
Factors to Consider in Undertaking a Patient Preference Study	Section V: p. 49	Overview of qualitative and quantitative preference assessment methods and discussion of how to select among the methods
Catalog of Methods for Assessing Patient Preferences for Benefits and Harms of Medical Technologies	Appendix A: p. 90	Detailed summary of quantitative preference assessment methods, including key considerations for method evaluation, and a critical review and examples (when available) of each method

Key findings of the study, which employed a discrete choice model, included:

- 61% of HHD patients would choose solo HHD over in-center HD
- More than 15% of HHD patients are already safely performing their treatments without a care partner
- Of the 85% of patients that perform HHD with a care partner, 16% dialyze solo at least part of the time

Source: [NxStage Home Hemodialysis Information for Healthcare Professionals \(Reference #24\)](#). The specific report is proprietary, but a publicly-available synopsis publication is in progress. See **Box 3** for more information about sample size and dissemination method and the [FDA 510\(k\) Clearance Letter](#).

NxStage also observed that some patients did not exhibit a preference for solo HHD based on the risks. They used that insight to guide their communications approach to ensure that the “right” patients get the therapy.

“We also developed a decision support tool to supplement the labeling and guide patients and clinicians on risk. We feel that solo HHD may not be for every patient – and our preference survey did indicate that. By having everything presented clearly, we are allowing the patient and the clinician to make an informed decision,” Snell said.

Box 3. Additional information about dissemination method and sample size

The survey was piloted with nine patients via phone to confirm understanding of the language used for the questions. Second, as an internal validity check, survey respondents were required to answer a test question to confirm understanding of the iconography used within the survey before being allowed to proceed through the questions.

Current HHD patients were contacted via email by a third-party vendor using unbranded communication and invited to respond to a survey about home hemodialysis. Each patient was provided a unique link for the survey to ensure that responses were not duplicated.

In total, 1049 patients were contacted electronically. Evaluable responses were received from 142 active HHD/in-center self-care patients, a 13.5% response rate. Respondents were required to be current HHD or in-center self-care patients who had completed training for HHD/in-center self-care.

Patients were offered compensation for completing the survey.

OUTCOME

NxStage included the patient preference study results in their 510(k) submission to the FDA and received clearance for the expanded indication of solo HHD during waking hours on August 24, 2017. This was the first 510(k) clearance to be based, in part, on patient preference data.

LESSONS LEARNED

Snell suggested that those device manufacturers interested in conducting a patient preference study first consider whether the study is truly warranted, for example, when further risk mitigation would make the device less usable,



more complex, take away functionality, or is not possible. Manufacturers can learn if that's the case by talking to their patients and knowing their market.

"Patient preference data are valuable and often generate new insights about a product. Beyond that, there are situations where the data are more than a 'nice-to-have' and they can serve as valid evidence for regulatory decisions. For example, a patient preference study may be appropriate for an indication, product, or therapy where there is some residual risk that a patient would accept, or some percentage of the population would accept, at certain levels and frequencies for the benefit," he said. "Then it becomes a question of how to quantify and label for that, so clinicians can eventually go ahead and treat."

If he had to sit down and plan the project in retrospect, he would advise manufacturers to take the following steps once they determine a preference study is warranted:

1. Identify the least burdensome route for quantifying preferences and developing the appropriate labeling

Collect and analyze some limited qualitative data, for example from focus groups, to understand what a small number of patients are saying. Did they validate your hypothesis? If so, make sure you have a large, representative sample of patients interested and available to participate in the quantitative study.

2. Review the MDIC Patient-Centered Benefit-Risk Framework

Use the MDIC PCBR Framework as a tool for understanding the science of patient input, including the FDA obesity study, discrete choice experiments, and insight into what to expect when bringing these study plans to the FDA.

Understand that the FDA obesity study was "the Cadillac" of patient preference studies because it compared several treatment options. Though it demonstrates an ideal model for a preference study, not all preference studies need to be that involved in terms of options. For many manufacturers, there may only be two options to compare.

3. In parallel, understand the regulatory pathway

The patient preference study is a tool to support a regulatory pathway. It's not the pathway. Answer in your own mind what the pathway will be and how the preference study will fit in. If you make it just about the tool, then you're "liable to be surprised with the overall submission pathway." Once the pathway is understood, go through the clinical protocol and project plan. Prototype the label and consider how the population surveyed in the preference study would translate to the labeling.

4. Discuss with FDA in a Pre-Submission Meeting

Request a pre-submission with the relevant disease branch. Be ready to demonstrate that the risk is one that cannot be further mitigated by better technology and that the benefits truly outweigh the risks for a well-defined group of patients.

5. Design, develop, and deploy the study

Develop a beta version of the survey and validate it before going live with the formal survey. Assemble cross-disciplinary teams and invest in external resources for study design and analysis, if necessary.

RESOURCES

[MDIC Patient-Centered Benefit-Risk Framework](#)

[First Steps for Sponsors Initiating A Patient Preference Study](#)

[FDA Patient Preference Guidance](#)



MDICx Webinar Series: - From stories to evidence: Quantitative patient-preference information to inform product-development and regulatory reviews – A three-part series

1. [When Is a Patient-Centered Case Needed for Regulatory Decisions and How Can You Build It?](#)
 - [Slides](#) | [Summary & References](#)
2. [Instrument Development: Example Applications and Lessons Learned](#)
 - [Slides](#) | [Summary & References](#)
3. [Data Analysis](#)
 - [Slides](#) | [Summary & References](#)

More about this case:

FDA Voice Blog: [How Patient Preferences Contribute to Regulatory Decisions for Medical Devices](#)

MDICx Webinar: [A Case Study in How Patient Preference Information Contributes to Regulatory Decisions for Medical Devices](#)



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