February 20, 2024

Dr. Jeff Shuren and Dr. Peter Marks
c/o Dockets Management Staff
Food and Drug Administration
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD 20852-1740

Re: Document number GUI00500012
Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices
Draft Guidance for Industry and Food and Drug Administration Staff

Submitted electronically at https://www.regulations.gov

Dear Drs. Shuren and Marks,

The Wound Care Collaborative Community (WCCC) would like to express its support and concerns regarding the draft Guidance Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products Guidance for Industry.

WCCC is a 501(c)3 non-profit, FDA-recognized collaborative community of over 150 wound care experts focused on improving the availability and accessibility of best practice care for people suffering with wounds. Our volunteer experts contribute their experience in clinical research, patient care, and development of devices, biologics, and drugs for patients with wounds. Participating members represent a wide range of healthcare practitioners, clinical societies, and associations in the fields of medicine, geriatrics, dermatology, podiatry, vascular, cardiovascular, plastic surgery, physical therapy, nursing, and research, as well as industry distributors, manufacturers, and product developers in both the US and international markets. More information about our community can be found at: http://www.woundcarecc.org/.

We value the attention the FDA is placing on the use of Real-World Data (RWD) and Real-World Evidence (RWE) as a basis for regulatory decision making. We believe FDA's openness to clarifying its approach to RWE in regulatory decision making and willingness to work with study sponsors as they develop real-world evidence that FDA regards as fit-for-purpose will encourage and accelerate the development of high-quality RWD/RWE. While we certainly understand the significant role that randomized controlled studies play in regulatory safety and efficacy decision making, we also believe there is also a significant role for real-world evidence which has not been fully considered to date. This stems mostly from a lack of clarity on what is and is not suitable for RWD and RWE for regulatory decisions. While the emphasis on RCTs as the primary source of acceptable evidence, the generalizability of RCT findings to real-world patients is often limited due to narrow inclusion and broad exclusion criteria among other artificial study conditions. Moreover, for wound studies, the only acceptable clinical endpoint by evidence assessors has primarily been total wound closure despite published

research that identified fifteen validated clinical endpoints as valid measures of performance[i] [ii] [iii]. Currently, these additional endpoints are more easily captured in real-world studies than RCTs although we support incorporation of the endpoints into both study types.

We find the use of specific examples clarifying how regulatory decisions such as labeling expansion requests may be based on real-world data to be useful and insightful. We also believe the templates for documentation and preparation for FDA Review in the draft Guidance will serve as excellent guides for real-world study sponsors.

We also welcome the expanded detail that was not present in the August 2017 Guidance on what RWD qualifies for "fit-for-purpose". That said, the Fit-for-Purpose outline (lines 906 -928) is still very general and contains no specific examples of RWD that would and would not be fit-for-purpose. Without more clarity on this point, the risk to study sponsors of investing considerable time and resources designing a RW study only to find it is not fit-for-purpose will continue to be high even if they understand other aspects of the RWE guideline. In our experience, the criteria for deeming a database fit-for-purpose are one the most misunderstood areas of real-world studies and one of the reasons conducting RW studies for regulatory purposes is not more frequently pursued by wound care developers and innovators. Without more clarity on fit-for-purpose in the final Guidance, we believe the value of the guidance document will be muted.

One of the challenges we see with real-world wound care studies is a lack of consistency and access to RWD across venues of care. Ensuring the data captured in a real-world database is reflective of patients' actual experience is a challenge for chronic wound patients particularly who tend to bounce between settings of care. Our group recently completed an extensive RWD landscaping project that assessed over forty-five real-world public and private wound care databases based on criteria developed for a second project involving in-depth real-world wound patient profiling. While the criteria were developed with a specific purpose in mind, they were not so unique that they could not be used for a variety of other study purposes. We found only a handful of RW databases that met the criteria or were 'ready, willing, and able' for use in third party research studies. Most databases were proprietary, lacked breadth of data captured, or had incomplete data fields rendering them usable only for internal benchmarking purposes. Given these findings, we are hopeful the section of the guidance on Data Quality and Reliability will help owners of RWD structure and maintain their databases such that their utility for regulatory-driven RW studies is more relevant, reliable and fit-for-purpose.

<u>Other Areas of Concern</u>

1. The RWE processes in the Guidance appear more complex than conducting an RCT despite the FDA statement that RCTs are more burdensome. We recommend flowcharting the processes outlined in the Guidance to the extent possible including pre-planning real-world studies and interacting with FDA CDRH/CBER real-world evidence review teams.

2. Under Relevance Definition, (1) Data availability Page 12 the Guidance suggests as an example the "Use of the device (e.g., the device identifier (DI) portion of the unique device identifier (UDI), …" is problematic for studies with wound care. The need for unique device identifiers (UDI) to identify specific product brands captured in real-world databases may be problematic for wound care technologies, as UDIs are generally available only on package labeling, but not on the devices themselves. This would not be a captured item in a registry or database.

3. Under Defining study design elements; (2) Development of conceptual and operational definitions for the study population, device, comparator, outcome, and covariates…Page 23…. "FDA considers the operational definition to include three components, as applicable: …one states – "Specific codes/component(s) assessed (e.g., via code lists)." We request clarification on the specific codes the FDA is referring to as claims data sources, depending on location of care delivery, may have various codes available such as diagnosis codes (ICD-10-CM), procedural codes (CPT® or ICD-10-PCM or HCPCS) and in some cases a HCPCS codes or UDI codes for specific devices or durable medical equipment codes.

4. Under Example 3: Control group, page 34 (Lines 1082 – 1095). At the heart of this analysis is matching a single-arm intervention study with a much larger "control" population using something like propensity score matching. We have learned, however, that many wound patients have other treatments besides Standard of Care (SOC) and that you should only match for a single wound type. In addition, when do you start? In a prospective trial it starts after the run-in period. Should we attempt to do the same with the control population?

   Further, the guidance states you need as many as twenty variables to do a proper match. The problem is that in wound care some of those variables would not have much data; for example, macro- or micro-ischemia; moreover, there are several ways of defining macro- or micro-ischemia and the techniques do not always give the same results. Selecting the "right" twenty variables is a challenge because of a lack of data even in good registries. There have been papers published in which propensity scoring matching or other methods were used that in hindsight were inadequate.

The Wound Care Collaborative Community appreciates the effort FDA is putting into clarifying and encouraging the use of real-world studies in regulatory decision-making. We also appreciate the opportunity to provide these comments to the draft Guidance. We welcome the opportunity to engage further with the agency in addressing the concerns shared in this letter.

Sincerely,

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[i] Driver V, Gould L, et.al., Identification and content validation of wound therapy clinical endpoints relevant to clinical practice and patient values for FDA approval. Part 1. Survey of the wound care community, *Wound Rep Reg* (2017); 1-12, DOI:10.1111/wrr.12533

[ii] Driver V, Gould L, et.al., Evidence supporting wound care end points relevant to clinical practice and patients' lives. Part 2. Literature survey, *Wound Rep Reg* (2018); 1-10, DOI:10.1111/wrr.12676

[iii] Gould L, Liu J, et.al., Evidence supporting wound care end points relevant to clinical practice and patients' lives. Part 3: The Patient Survey, *Wound Rep Reg. (2020)*; 1–10, DOI: 10.1111/wrr.12872