

BENECHILL

November 21, 2006

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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2006D-0331

This letter is to provide comments to Docket No. 2006D-0331 regarding FDA's Draft Guidance for Exception from Informed Consent.

As medical device developer and manufacturer, BeneChill, Inc. will rely on the exception from informed consent regulations and guidance document to evaluate the safety and effectiveness of our technology for therapeutic hypothermia in intervening cardiac arrest, acute stroke, and traumatic brain injury. Clearly, few if any of these prospective patients will be capable of providing informed consent. Although informed consent from a prospective patient's legal guardian will be sought whenever possible, these emergent conditions frequently occur when a legal guardian cannot be reached within the window in which we intend to test our products.

Therefore, the exception to informed consent regulations and guidance document are critical to our ability to evaluate the safety and effectiveness of our technology designed to treat these critical care patient populations. BeneChill will only address questions of primary concern in this commentary. For convenience, FDA's original question is repeated before BeneChill's response.

Public Disclosure Prior to Initiation

(12) Are there certain types of information (e.g., adverse event reports, study protocol, informed consent document) that should, at a minimum, be publicly disclosed to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn?

The depth of information already disclosed to the public and/or targeted communities, e.g., the informed consent form or a study synopsis such as those published on the clinicaltrials.gov internet site is sufficient. Both sources of information could be appropriately used for public disclosure as well as community consultation efforts.

It is not appropriate to require public disclosure of the entire sponsor protocol, however. Sponsor protocols frequently contain proprietary information such as product testing or information on mechanism of action. In addition, the details of the study design and statistical analysis plan are included in the protocol. These types of information are proprietary and closely guarded by study sponsors. Furthermore, just as the FDA may not disclose sponsor proprietary information (21 CFR 812.38(d) and 21 CFR 814.9), the FDA can not compel a sponsor to

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disclose proprietary information. Requiring disclosure of this type of information would be in conflict with the confidentiality provisions upon which study sponsors rely for protection of information that ultimately reveals a company's intellectual property and business plans.

The informed consent document is a good source of information because it is already distributed to individuals not associated with the company: the patients. These informed consent documents are comprehensive, containing information on the product, the condition under study, the number of patients and sites involved, the risks and possible benefits of participation, the randomization scheme, if any, the right to decline participation, etc., as required in 21 CFR 50.25. Because the informed consent document is so comprehensive, this the only study-related information that the regulations require a prospective study subject to receive. To require community information beyond that which is supplied to the person most impacted by the study would suggest that the informed consent provisions are inadequate. The community need for information can not be stronger than the needs of the patient actually receiving the treatment.

It is likewise inappropriate to disclose adverse event reports to the public or targeted communities. Adverse event oversight in the form of an independent Data Safety and Monitoring Committee is already required by regulation for any emergency clinical research. Furthermore, the life-threatening nature of conditions that qualify for informed consent exceptions can lead to a cascade of adverse events not well understood by the general public. Providing this type of information could cause unfounded concern and jeopardize the future of a viable technology with the potential to provide improved health care.

If adverse event reporting were determined to be necessary, it would be inappropriate to release individual adverse event reports to the general public. As members of the scientific community, we would not expect a DSMB, IRB or the FDA to review individual adverse events without context. We should therefore guard against this possibility in the general public. Examining individual adverse events could cause unwarranted alarm in those not familiar with the significant morbidities associated with these life-threatening conditions. If adverse event reporting is needed, a more appropriate format would be a summary report, the appropriate level of summary information defined by the FDA to provide clarity of requirements and to ensure consistency across studies.

(13) Should the full protocol, or other information such as the investigator's brochure, for emergency research be available to the general public before initiation of the clinical investigation?

The investigator's brochure often contains proprietary information beyond that provided in the study protocol. For the reasons described in the response to Question #12 above, neither the full protocol nor the investigator brochure should be made available to the general public.

Public Discussion of Emergency Research

Is there a need for additional review and public discussion [regarding emergency research protocols?]

Current regulations governing IRB review and community consultation, as well as the significant efforts of the FDA during the review process provide sufficient protection of the rights, safety and welfare of potential study subjects and the community. IRBs, communities and the FDA are already free to consult with experts as they see fit so that unusual or difficult issues can be resolved with existing mechanisms. It is therefore unclear what value a required panel/expert

review would add. Additionally, this would require another unnecessary step and slow down the approval process. Another important consideration is that such a panel/group of experts would be unlikely to take into account local issues that are most appropriately handled through the community consultation activities. Indeed, such a panel/group of experts could make recommendations that are later revealed to be unworkable or impractical for a particular community.

Additional Challenges

(20), (21) Are there any additional challenges to the conduct of emergency research that have not been identified. If so, what are they, and how should they be addressed?

The regulations and guidance document indicate that any patient (or legal guardian) may withdraw from any investigational study at any time. This element of informed consent is critical but should be modified for certain types of emergency research. By the very nature of emergency research, the intervention is acute and must be made within a restricted time frame. If the exception to informed consent is used, the subject will undergo the intervention under study. Current informed consent regulations would require the investigator/sponsor to stop collecting data the moment a patient withdraws from a study. For this type of research, however, withdrawal of consent *after* the intervention would restrict investigators from accessing outcomes data in the medical record for that subject.

Access to the medical record to extract outcomes data following an emergency intervention is vital in these subjects. Attrition in enrollment due to this restriction could make trial sizes unreasonably large. More importantly, however, restriction to outcomes data could mask an adverse safety signal that would otherwise be detected earlier.

One solution would be to discontinue therapy or treatment upon withdrawal of consent but to collect a limited number of predefined critical outcomes measures after withdrawal of consent (e.g., severe adverse event, unanticipated adverse device effect, death). The existing community consultation mechanism would provide critical oversight to the acceptability of collecting this data. HIPAA regulations would also serve to ensure that the privacy of all subjects is maintained.

Conclusion

BeneChill supports the FDA regulations and guidance document on exceptions to informed consent. However, many of the questions posed by the FDA seem to contemplate unnecessary incremental requirements for this process. Existing mechanisms are sufficient to protect the rights, safety and welfare of patients who can not provide informed consent. Rather than adding to the existing requirements, it would be helpful for the FDA to clarify the existing guidance document to achieve greater clarity in requirements and processes.

BeneChill, Inc.

Respectfully submitted,

BeneChill, Inc.

A handwritten signature in black ink that reads "Nora K. Hadding". The signature is written in a cursive style with a large, prominent initial "N".

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