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## The Study from Hell

**By Norman M. Goldfarb**

The following letter is a complete and accurate version of the original except for changes to protect the identities of the parties involved and fit the story's theme.

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# Orpheus Research

Thanatos Hecate, M.D.
HadesPharma, Inc.
1 Styx Road
Cerberus Station, HE 99999

December 17, 2002 BCE

Re: REBIRTH Vaccine Study

Dear Dr. Hecate:

I would like to share with you some of the obstacles that have interfered with our performance of the REBIRTH vaccine study.

1. **Our enrollment period was compressed to just 22 workdays, from 10/14 to 11/12, allowing us to enroll only 57 subjects despite a Herculean effort.**
    - We submitted our 1572 to CharonCRO, the CRO, on July 15, 2002 BCE. We did not receive IRB approval until October 2, 2002 BCE.
    - Shipping problems caused additional delays and distractions:
        - Our contract was sent to another investigator. We did not receive our copy to sign until September 24 despite numerous requests. This delay held up shipment of our regulatory binder.
        - We then received another investigator's regulatory binder. We returned them. CharonCRO did not ship ours until October 3.
        - Shipment of the co-vaccine vaccine was delayed by "a paperwork screw up." We did not receive co-vaccine until October 11.

2. **Visits by site monitors and auditors consumed substantial blocks of time and interfered with our ability to perform the work they were reviewing.**
    - Five different monitors and auditors were on-site for seven of the 22 workdays during our enrollment period.

3. **We did not receive proper training, despite repeatedly communicating our intention to enroll over 100 subjects with multiple satellite sites.**
    - HadesPharma was unwilling to pay for Dr. Orpheus (along with at least one other west-coast investigator) to attend the entire Investigator Meeting. As a result, he missed, for example, training for arm randomization.
    - Training at the initiation visit was perfunctory and delivered in a casual manner in a busy office by an inexperienced site monitor. We learned of her inexperience when she was subsequently accompanied to the second visit by a trainer. (For example, she incorrectly trained our CRC to not randomize vaccinations by arm. Her explanation was that Dynomor vaccinations in the left arm would minimize potential problems for right-handed patients. She did not notice the problem when we demonstrated our procedures to her in detail at the second visit.) She was aware that our coordinator on the REBIRTH study had not attended the investigator meeting.
    - The initiation visit occurred on September 10, ten days before CharonCRO shipped source and other documents to us and over a month before we received the vaccines and randomization cards.
    - Because of IRB, vaccine, contract, regulatory binder and other delays, there was a gap of over a month between training by the site monitor on September 10 and first subject enrollment on October 14.
    - We enrolled 44 subjects by the time of the first monitoring visit, thereby making small problems into large ones.

4. **The initial site monitor did not perform adequate site monitoring.**
    - CharonCRO assigned an inexperienced site monitor. She was accompanied by a trainer who apparently was not well-versed in the protocol.
    - At the first monitoring visit, the site monitor(s) did not hold a wrap-up meeting.
    - The site monitor did not inform us of her findings until 13 days later (allowing us only one workday to address issues before the auditor/second monitoring visit).
    - We are puzzled as to why the original site monitor sent us a letter dated November 16, 2002 BCE stating that the change in site monitors was "strictly for administrative purposes at CharonCRO." The replacement site monitor had arrived five days earlier per our request for an experienced replacement site monitor. The new site monitor, by the way, is entirely satisfactory.

5. **We were strongly encouraged by HadesPharma and CharonCRO to quickly enroll large numbers of subjects, all the way through November 8, 2002 BCE.**
    - We were certainly under no obligation to comply, but this encouragement strongly influenced our priority of focusing on enrollment.
    - HadesPharma and CharonCRO continued to press us for more enrollment despite being well-aware that our limited staffing had fallen well behind in documentation.

6. **Based on the above pressure, along with CharonCRO's assurances that IRB approval was forthcoming, and that the vaccines would arrive when promised, we scheduled and cancelled, at the last minute, five full days of enrollment visits.**
    - Rescheduling wasted time, created confusion, and caused two sub-investigators and numerous patients to not participate in the study.

7. **Medically-untrained site monitor disputed the opinions of two physicians as to the ability of nursing home residents to give informed consent.**
    - A neurologist has confirmed the mental competence of all six nursing home residents.
    - Due to concerns raised by the site monitor, HadesPharma and CharonCRO, at the last minute, cancelled a full enrollment day at an intermediate care facility (not a nursing home).

8. **The following issues consumed time and distracted us during critical periods. Furthermore, these issues caused us to lose confidence in the protocol and rely instead on (sometimes erroneous) verbal guidance.**
    - Inclusion factor #7 does not define "symptomatic heart failure", specify qualifying medications to control shortness of breath, or specify conditions in which a diuretic, for example, is a qualifying medication.
    - Consent document does not disclose risks of the co-vaccine.
    - Consent document does not disclose risk of cardiac arrest due to epinephrine hypersensitivity. Alternatively, the presence of a cardiac conduction problem should have been an exclusionary criterion. (Note: We discovered this life-threatening risk only because of the thoroughness of our consenting process.)
    - The protocol and source documents state no safety purpose or request any adverse event information for the weekly surveillance calls.
    - The protocol does not specify the appropriate interval between follow-up surveillance call attempts.
    - The protocol does not explain what to do with the 14-day diary if death occurs during first seven days (while subject is still completing the 7-day diary).
    - The protocol does not explain what to do if a subject dies a second time.
    - The protocol requires that concomitant medication information be collected at Visit #1 but the concomitant medication source document is provided for Visit #2.
    - Instructions in the regulatory binder for processing blood are incorrect.
    - The replacement vaccine randomization codes are visible when the replacement card is held up to the light.

9. **Conflicting, incorrect and incomplete guidance that we received on this study included:**
    - The protocol does not define the beginning of "Week One" for surveillance calls. Initial guidance from CharonCRO was that weeks begin on Mondays. Subsequently, CharonCRO advised us that weeks begin on day eight, except on Mondays if day eight falls on a weekend.

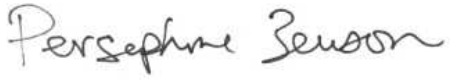
- CharonCRO sent us a "List of Qualifying Medical Conditions", then instructed us to ignore that list, and then sent it to us again. In the end, HadesPharma distributed to the other sites the list that we created.
- CharonCRO advised us that additional study personnel, with proper training, could obtain informed consent, provided we added that role to the Site Signature List. No mention was made of the requirement to inform the central IRB.
- CharonCRO instructed us to not list nursing homes on the 1572 at satellite sites (because they are just residences), then to list them, and then to not list them.
- The protocol says that trade names for concomitant medications are preferred. CharonCRO then said we had to use them.
- The protocol requires illness visits on Day 1 +3. CharonCRO first instructed us that illness visits are required in the first 24-72 hours (Day 1 +2). CharonCRO then instructed us that illness visits are required if an infection occurs outside the 72-hour window provided the subject is symptomatic.

The above issues consumed huge amounts of staff time and distracted our attention when we could least afford it.

Dr. Orpheus turned his practice upside down to enroll 57 subjects, address countless issues, and respond to changing requirements. I am personally awed by the work he has done. You are probably not aware that, during the enrollment period, and without any complaint, he also (a) played a major role in treating his mother, hospitalized for an extended period with a serious illness, (b) dealt with the birth of his first child, (c) dealt with the stroke and incapacitation of his housekeeper, (d) hired a replacement nanny, (e) dealt with the illness of his aunt, for whom he is conservator, (f) dealt with his father's serious illness, and (g) dealt with the death of his dog.

I hope the above information is useful to you in designing future studies. We worked extremely hard on this study in good faith and with the best of intentions.

Yours truly,



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Site Manager

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