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Rapid response to:

Covid-19: Researchers face wait for patient level data from Pfizer and Moderna vaccine trials

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Effect of mRNA Vaccine Manufacturing Processes on Efficacy and Safety Still an Open Question

Dear Editor,

Recent calls for more transparency in COVID-19 vaccine clinical trials is particularly relevant for data on the manufacturing process, which is an integral part of the regulatory approval process to ensure consistent safety and efficacy outcomes.[1,2]

An October 2020 amendment to the protocol of the pivotal Pfizer/BioNTech BNT162b2 (Comirnaty) clinical trial (C4591001) indicates that nearly all vaccine doses used in the trial came from 'clinical batches' manufactured using what is referred to as 'Process 1'.[3] However, in order to upscale production for large-scale distribution of 'emergency supply' after authorization, a new method was developed, 'Process 2'. The differences include changes to the DNA template used to transcribe the RNA and the purification phase, as well as the manufacturing process of the lipid nanoparticles. Notably, 'Process 2' batches were shown to have substantially lower mRNA integrity.[4,5]

The protocol amendment states that "each lot of 'Process 2'-manufactured BNT162b2 would be administered to approximately 250 participants 16 to 55 years of age" with comparative immunogenicity and safety analyses conducted with 250 randomly selected 'Process 1' batch recipients. To the best of our knowledge, there is no publicly available report on this comparison of 'Process 1' versus 'Process 2' doses.

Two documents obtained through a Freedom of Information Act (FOIA) request[6] describe the vaccine batches and lots supplied to each of the trial sites through November 19, 2020[7] and March 17, 2021,[8] respectively. According to these documents, doses from 'Process 2' batch EE8493Z are listed at four trial sites prior to November 19, and four other sites are listed with 'Process 2' batch EJ0553Z in the updated document. Both batches were also part of the emergency supply for public distribution. The CDC's Vaccine Adverse Event Reporting System, known to be underreported,[9] lists 658 reports (169 serious, 2 deaths) for lot EE8493[10] and 491 reports (138 serious, 21 deaths) for lot EJ0553.[11]

Furthermore, additional 'Process 1' batch EE3813 doses with distinct Pfizer lot numbers were added to the later batch document[7] at over 70% of trial sites, potentially supplied at a later stage to enable vaccination of placebo patients with BNT162b2. The 6-month interim clinical study report[12] from the Comirnaty trial notes that "the IR for any AE and at least 1 related AE and severe AE for participants who originally received placebo and then received BNT162b2 are greater (205.4 per 100 PY, 189.5 per 100 PY, 6.0 per 100 PY) than the IRs (83.2 per 100 PY, 62.9 per 100 PY, 4.3 per 100 PY) for participants who originally were randomized to BNT162b2" (p222). It is unclear whether there is a connection between the lots administered to the crossover placebo subjects and the elevated rate of AE's.

Finally, a recent study found significant variability in the rate of serious adverse events (SAEs) across 52 different lots of Comirnaty marketed in Denmark.[13] This finding underscores the importance of understanding better the potential impact of variability in the production process of COVID-19 mRNA vaccines on efficacy and safety.

Evidence from existing research and trial documents highlights the importance of publicly disclosing the analysis comparing reactogenicity and safety of process 1 and 2 batches as specified in the trial protocol, and more generally patient-level batch and lot data from the trial.

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