Clinical Trial Related Aspects during COVID

Case study of an Alzheimer's disease (AD) international trial successfully initiated during the first wave of the COVID pandemic

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Organization of Presentation

- Introduction
- Background and setting (US and International)
- Shifting planning given the emerging situation
- … and serendipity sometimes assists
- Early recommendations for enhanced site activities [re:COVID]
- Site Survey on COVID related practices: US and UK/EU site perspective
- Corollary: AD and COVID interactions
- Summary

Introduction: We are working in an evolving situation: the US has lead the resumption of trials and non-US countries remain in flux

- As of Jan. 25, 2021, GlobalData found that 929 disrupted trials have resumed and, out of these, 71.9% are currently recruiting participants, 12.8% have completed recruitment but are still ongoing and 0.5% of trials have yet to start recruiting subjects.
- “There is a slight, steady increase of trials resuming activity, with the initial general trend showing a gradual increase in the overall percentage of trials for each trial status,” said Priya Nair, a trials intelligence analyst at GlobalData.
- “However, between December 23 and January 25, ongoing recruiting trials decreased from 74.6% to 71.9%, and completed trials increased from 10.6% to 12.8%. The majority of trial disruptions can be attributed to patient safety measures, strict lockdown requirements, social distancing procedures and the high demand on medical professionals to treat COVID-19 patients.”
- Geographically, the U.S. has the highest number of resumed trials at 87.5%, followed by the U.K. at 10.8% (which has issued national lockdowns since December amid its new strain), Spain at 9%, France at 8.8% and Germany at 8.1%.
- This was not the situation in early 2020 where the majority of AD trials were placed on hold…..

The feeling of initiating an Alzheimer's disease trial during the first wave:

When the Sponsor instructions are:

"When a place cannot be passed, it necessary to pass. It is precisely that." (From A.F. Mummery)

Background and Setting

- Rescue study
  - Many site changes necessary, issues with TMF transfer from previous partner, etc.
- 5 Amendments (and more during this period)
- EMEA ruling necessitated changing primary outcome
- Increased geographic distribution due to increased patient numbers
- Essentially a “re-start” in January 2020
- Directly into the headwinds of COVID-19

Shifting planning….

- Sites were highly motivated both from a patient and a financial perspective
- Sponsor wished to continue to move forward – we were able to ensure enhanced safety procedures were put in place and documented before re-engaging the sites
- Excellent previous relationship with many sites helped in several ways: lines of communication open, transparent exchange of information from both parties.
- Some sites, as soon as able, wished to resume activities (after several months of hiatus): these were prioritized
- Also prioritized were activities such as site readiness, a highly efficient path when sites were able to resume activities.

…and serendipity

- Almost no other AD trials being run simultaneously, we hit a “sweet spot”
- Initiated when several other large trials were ending or had recent failures (particularly related to amyloid based trials)
  - Aducanumab, gantenerumab, solanezumab [Caveat: this has recently changed]
- From the patient and family perspective, the neurodegeneration of AD is continuous, the later the intervention, the less likely it might prove effective
- Families of AD patients, when circumstances permitted, wished to continue treatment in the trial
- Retention was enhanced (better than predicted in most AD trials given the circumstances)

Enhanced site activities

- Required detailed COVID protocols put in place; site and patients must feel entirely safe. Used assisted/private transportation when necessary
- Allowance for remote assessment of (primary) outcome scale when necessary
- Adapted remote site visit: luckily all site qualification visits were completed before major lockdown occurred.
- Informed Consent: due to data protection/privacy rules the IC review could only be held onsite and this review remained incomplete in some countries
- Remote visits largely occurred in the US vs the EU. When COVID rates sufficiently decreased after first wave, a number of on site visits were able to be conducted. Sites and monitors remained in constant communication and remained flexible
- SDV has occurred in the US, less so in UK/EU sites. Remote monitoring visits remained in place and utilized dependent upon country/state open status
- Grant payments were kept exceedingly timely which kept sites in “positive cash flow” state
- From Jan 2020 to Jan 2021, the US and Poland were outstanding contributors of patients

Survey queries (sent to top enrollers)

- *What changed in your practices between pre and mid COVID periods?*
- *What do you attribute your successful recruitment to during COVID?*
- *What do you attribute your successful retention to during COVID?*
- *Were patients/family members first asked if they were still willing to come to clinic visits?*
- *Were the enhanced safety protocols at site explained to them before they agreed to continue? What was the generally the outcome of this conversation?*
- *Out of 100% of your patients, how many declined in % to participate due to COVID?*

Survey results: (10 sites) 1/3 slides

- *What changed in your practices between pre and mid COVID periods?*
  - **US(4):**Phone "screen" prior to visit to assess potential COVID symptoms, upon arrival at site vitals taken first (no fever) before proceeding; appointments spread out, essential staff only, longer procedural time for sanitizing continuously; halted new screens temporarily; communication of new procedures with patient/partners
  - **UK(1):**Careful scheduling of visits; all gov.UK and PHE guidelines and CQC requirements followed
  - **SP(2):**Home visits established when permitted, telephone visits when possible, more time for in-clinic visits, avoidance of waiting outside hospital/clinic
  - **IT(1):**Reduced number of visits, as much remote data collection as possible
  - **FR(1):**Increase in social distancing, following local governmental guidelines, otherwise, no extreme changes in how patients followed
  - **POL(1):**Fewer patient visits, PPE, social distancing, sanitizing regularly
- *What do you attribute your successful recruitment to during COVID?*
  - **US:**Quick adaptation to circumstances, more reliance on advertising (costing more), outreach became online vs direct, greater funnel for cancellations: more effective screening; positive experiences shared with others, transparency and precautions taken
  - **UK:**Communication of safety precautions, flexibility of Sponsor for private transportation
  - **SP:**Sensation of safety, time between visits extended; "Neurodegeneration does not stop because of COVID"
  - **IT:**Collaboration from referring clinics to AD specialists
  - **FR:**No major changes
  - **POL:**Continuous open status of clinic and no break in patient visit flow

Survey results:2/3

- *What do you attribute your successful retention to during COVID?*
  - **US:**Continual attention to patient safety and education and safe; no crowding or waiting for appointment; transparency of safety process; attention to subject comfort
  - **UK:**Compliance to all new guidances shared with patients, reassurance and communication open; use of private transportation
  - **SP:**Continual follow-up at with patients, direct phone contact with nurse 24/7; disease awareness
  - **IT:**NA
  - **FR:**Stability of clinic and procedures
  - **POL:**Continual contact with patient/partners
- *Were patients/family members first asked if they were still willing to come to clinic visits?*
- [All countries had similar replies, therefore bundled]
  - Many instituted 2 step confirmation process: Prior to each visit, patients called and reconfirmed willingness and appropriateness to continue, then 24 hours prior to visit, COVID symptom checklist collected
  - Continual education about social distancing, isolation practices and avoidance of unnecessary travel and contact comforted patient/partner regarding safety precautions

Survey Results (3/3)

- *Were the enhanced safety protocols at site explained to them before they agreed to continue? What was the generally the outcome of this conversation?*
  - **US:** Yes, thoroughly and open communication tantamount to continued participation; gratitude for explaining so carefully the new procedures although more time needed overall
  - **UK:** Yes and many patients expressed their reassurance in the process
  - **SP:** Yes, patient felt at ease in their safety at the clinic
  - **IT:** Yes, simple explanations were helpful and accepted
  - **FR:** Generally little change in procedures
  - **POL:** Yes, positive feedback on attention to their safety
- *Out of 100% of your patients, how many declined in % to participate due to COVID?*
  - **US:** 2-10%; new screens decreased by 35% for several months then returned to normal
  - **UK:** 10-12%
  - **SP:** 0%
  - **IT:** 25%
  - **FR:** 0%
  - **POL:** 10-15%

Corollary: AD and COVID interactions

- Chronic systemic inflammation is considered to be of the underlying pathogenic mechanisms involved in AD
- The inflammation related to viral infection significantly worsens tau-related pathology and results in spatial memory deficits in animal models
- In these models, the hippocampus is especially vulnerable to respiratory viral infections; infection with influenza significantly affects LTM.
- Cytokine responses to viral infection are significant and possibly lead to the over-production of pro-inflammatory cytokines
- In the presence pro-inflammatory cytokines, microglial cells loose their capacity to phagocytize B-amyloid (overproduction of B-amyloid being a hallmark of AD)
- Will COVID infection hasten neurodegeneration in those who are at the tipping point of AD and accelerate the AD cascade in the diagnosed?

Summary

- Covid-19 is still not fully behind us; Every country has/had distinct responses to the outbreak in their own manner
- Overall, the dedication and determination of sites and patients with AD persevered throughout the initial phases of the pandemic
- E.g., “Neurodegeneration does not stop because of COVID” summarized that patients/caregivers as participants were willing to move forward with AD trials (in an early AD population)
- Clinical AD practices have changed to more remote interactions worldwide
- There is a negative interaction with COVID and the AD populace