Cicely Saunders International
Better care at the end of life

BETTER-B

KING'S College LONDON

## Better Treatments for Breathlessness in Palliative and End of Life Care

# BETTER-B trial processes and delivery


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# DISCLOSURE

- Name: Adejoke Oluyase
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- Relationships with for-profit and not-for-profit interests:  None
- Grants/Research Support:  Medical Research Foundation
- Consulting fees: None
- Other (including employment): None

# The BETTER-B Trial

- **Design:** International, multicentre, Phase III, double-blind, randomised, placebo-controlled trial.

- **Funding:** The European Union's Horizon 2020 Research and Innovation Programme under grant agreement No. 825319.

- **Participants:** COPD, ILD patients with Modified Medical Research Council Dyspnoea Scale grade 3-4
  - Grade 3 (I stop for breath after walking about 100 yards or after a few mins on level ground) or
  - Grade 4 (I am too breathless to leave the house or I am breathless when dressing or undressing)

- **Procedures:** Randomised 1:1 to oral mirtazapine 15mg/day or placebo, assessments at baseline, day 7, 14, 28, 56, 180

- **Clinical end points (at 56 days)**
  - 'Worst' and 'average' breathlessness over the past 24 hours using NRS
  - Chronic Respiratory Questionnaire (CRQ)
  - Integrated Palliative care Outcome Scale (IPOS)
  - Hospital Anxiety and Depression Scale (HADS)
- **Qualitative interviews & health economics**

# BETTER-B Main Trial Objective

- To determine whether mirtazapine (a repurposed medicine) is an effective treatment for the reduction of self-reported worst breathlessness (as measured by a numerical rating scale (NRS)) at 56 days post start of treatment compared to placebo in patients with COPD or ILD.

# BETTER-B Sites

12 sites in **Europe**:

- 3 UK sites
- 3 Italian sites
- 3 German sites
- 2 Ireland sites
- I Poland site

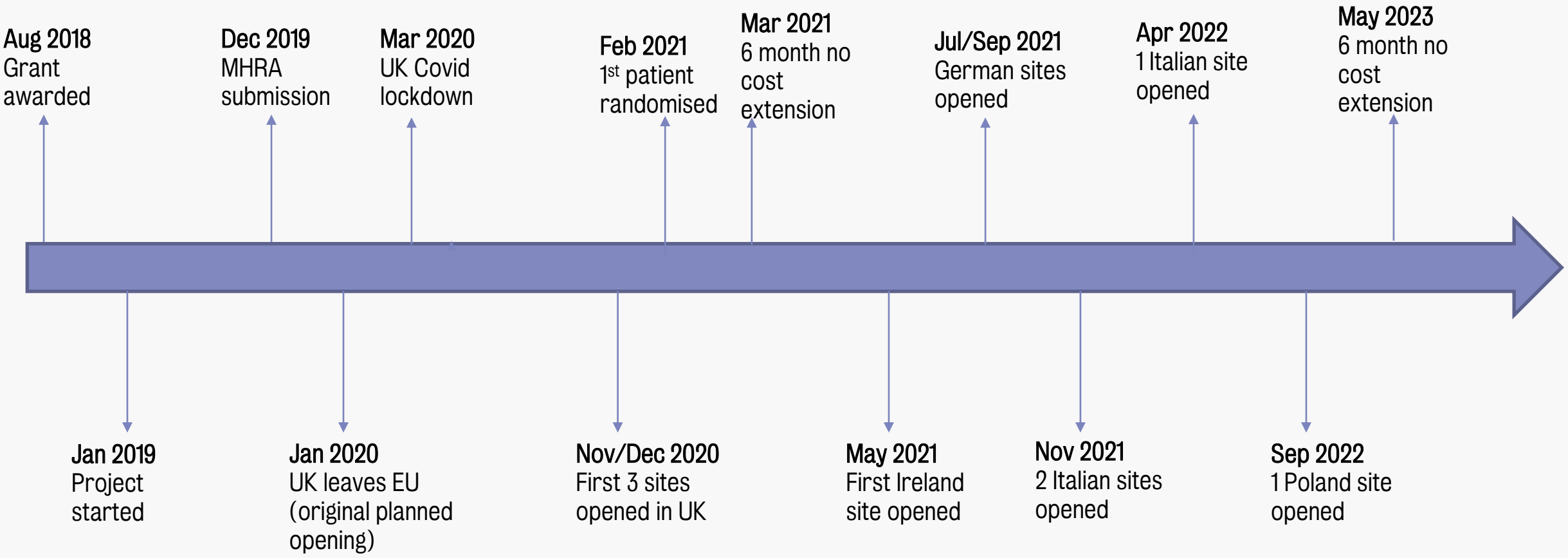
**Parallel Study** in Australia using the same protocol but sponsored by the University of Technology Sydney, funded by the NHMRC – European Union under Application ID: APP1170731.

**Numbers recruited:**

272 UK/EU participants (205 patients/67 caregivers)

28 Australia/New Zealand participants (20 patients/8 caregivers)

# BETTER-B Timeline



# Sponsorship & contracting

| Risk No. | Description of risk | Level of risk | WP(s) involved | Proposed risk-mitigation measures |
|---|---|---|---|---|
| 1 | UK leaving the EU in 2019 (Brexit) – current uncertainty regarding UK legislative requirements and status of UK sponsor within EU post Brexit. | High | 2-5 | Co-sponsorship between KCL and UCD will ensure all regulatory and legislative requirements for clinical trial conduct will be met in both the EU and UK post Brexit. |
| 2 | Implementation of Clinical Trials Regulation in 2019 across EU prior to start of Clinical Trial. | Low | 2,3 | Co-sponsor UCD based in EU will manage EU Portal requirements. |

# Sponsorship & contracting

- BETTER-B: clinical trial of an IMP, Clinical Trial Authorisation (CTA) Applications were submitted to medicines regulators in participating countries.

- Different legal requirements in EU countries e.g co-sponsorship not allowed in Germany

*** KCL could not be added to the CTA forms for European Sites**

- Ireland: KCL designated as having contractual responsibilities
- Poland: KCL designated as having contractual responsibilities
- Italy: KCL designated as having contractual responsibilities

# Regulatory & ethics submissions

- Different systems e.g. own portals for uploading CTA
- Lack of information in English
- Use of fax!
- Working with local PI/team

# Regulatory & ethics submissions

- At the initial stages, regulatory authorities in Italy, Germany and Poland were not accepting non-Covid applications. Germany wasn't submitted until Aug 2020 and Italy March 2021. Poland was submitted in May 2021.

- CTA resubmission occurred in both Ireland and Germany to allow for UCD to be designated as the main sponsor.
- In Italy, 4-month delay between CTA submission and trial approval due to complications in IMP arrangements post-Brexit (required 2 rounds of submission).
- In Poland, 13 month delay between CTA submission and trial approval (required 4 rounds of submission)
- Apart from the UK, ethics applications were delayed in the other EU countries as they prioritised Covid-related applications.

# Response times for CTA approval

| Countries | Formal CTA timelines during trial | Actual CTA timelines during trial |
|---|---|---|
| Germany | 30 days | 46 days |
| Italy | 60 days | 65 days (provisional), 117 days (full) |
| Ireland | 25 days for first response, 60 days total | 45 days |
| Poland | 60 days | 13 months |
| UK | 60 days | 42 days |

# Challenges experienced and mitigation measures

| Challenges | Mitigation measures |
|---|---|
| •Covid-19 and its recurrent waves<br><br>➢ Participating countries de-prioritised non-Covid research<br>➢ Fear of infection by participants/reluctance to visit hospital<br>➢ Staff diversion to Covid-related work<br>➢ Staff shortage/overworked staff<br>➢ UK R & I pause to recruitment<br><br>•Remote clinics/closure of clinics<br>•Trial eligibility criteria<br>•Brexit<br>•Delays in receiving the IMP due to a worldwide shortage | •Allowed for remote consent and follow-up<br><br>•Opened additional PICC sites at KCH and an addition site in Ireland.<br><br>•Applied for a 12 month no-cost extension<br><br>•Removed cardiovascular exclusion from protocol as this impacted recruitment<br><br>•Co-sponsorship between KCL and UCD<br><br>•Worked with Modepharma to source another supplier |

# Other strategies to increase recruitment

- Regular meetings with sites to provide support
- Presentations to clinical teams at meetings
- Rewarding good practice e.g monthly newsletter showcasing sites meeting their monthly targets.
- Posters in clinics
- Newsletters etc

# Translation

- Participant-facing documents were translated (PIS, consent form, subject diary, GP letter).

- Questionnaires were reviewed to check those that were translated and validated in other languages. Where these were not available, forward and backward translations were carried out.

# BETTER-B Translations

**Documents to be translated** = All participant-facing documents (PIL, consent form, questionnaires, subject diary, GP letter)

Local teams translated English master document into native language **(forward translation)**

Local teams made changes necessary for local ethics approval

e.g removal of collection of race/ethnicity data in Germany

Changes sent to Sponsor for approval

# BETTER-B Translations

Forward translated document translated into English **(backward translation)**

All translations completed by one team member, and reviewed by another team member

Translation certificates for forward & backward translations

Sponsor compared backward translation to English master documents & checked certificates

**Aim: ensure faithful translation to ensure patients received the correct information**

# IMP

- Sourcing a product licenced in an EU country for no-deal Brexit
- Absence of production staff & prioritisation of Home Office listed products
- Increased storage costs
- Post Brexit QP release & shipment

# Patient and Public Involvement (PPI)

- PPI involvement from inception
- Reviewing participant-facing documents
- Shaping the language and content of the BETTER-B website
- Co-design of dissemination strategy
- Patient involvement in the TMG and TSC

# Key reflections

- Cross-national research is important in developing the evidence base.

- The new EU Clinical Trials Information System (CTIS) is a co-ordinated system that should help future trials.

- BETTER-B question though central to Covid-19 was de-prioritised. Palliative care should be a core part of health emergency.


thank
you!