

# Support of an ethics advisory board in a large international research programme on severe breathlessness in advanced respiratory diseases (BETTER-B)

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## Background

Severe breathlessness is burdensome and frightening to patients and their families, and results in high health and social costs. Given the need for new treatments for severe breathlessness, drug repurposing offers a possible approach. However, it is paramount to carry out ethically rigorous research in a vulnerable population whose clinical status may be deteriorating. The European Union (EU, funder for BETTER-B) required the formation of an independent Ethics Advisory Board (EAB) to oversee all ethical aspects of the BETTER-B programme.

**Aim:** To describe how an EAB was proactively integrated into the BETTER-B programme to guide ethical conduct, address emerging ethical complexities, to mitigate both ethical and broader contextual challenges.

## Method:

An EAB with international ethicists and ethically engaged clinicians was convened as per EU requirements. BETTER-B included a clinician survey, a double-blind, randomised, placebo-controlled trial in seven countries, and clinical guidance. Patient and Public Involvement and Engagement were embedded throughout, also partnering with the European Lung Foundation. Three ethics reports submitted to the EU, alongside EAB minutes, were analysed using content analysis.

## Results

The EAB was embedded from conception and design at all stages through to programme dissemination and knowledge mobilisation. This expanded beyond regulatory and governance processes to include real-time involvement in decision-making and trial management, particularly within the context of Brexit and the Covid-19 pandemic.

The EAB guided the BETTER-B team in navigating ethical and operational challenges, including actions to minimise risk and uphold patient and caregiver voices in decision-making. It provided advice on maintaining equipoise in trial conduct and communication; addressed concerns over potential financial hijacking of mirtazapine; and contributed to defining optimal treatment parameters. It wrote in support to the EU to continue the study. It discussed when to stop recruitment to allow for robust analysis and reporting and the implementation of unblinding. The EU commended the role played by the EAB in BETTER-B.

## Results: extracts from reports and minutes

### Promotion of the BETTER-B Programme

The EAB advised that the BETTER-B team had an important role to play in communicating the BETTER-B programme with interested stakeholders including researchers, clinicians, patients, family, members of the public and potential participants. The EAB suggested that the promotion of the BETTER-B programme should focus less on the main trial and more on the overall programme of work and evidence base leading to this project. The EAB were concerned that if not carefully considered, emphasis may be placed on the pharmacological management rather than non-pharmacological management of breathlessness. Despite the main trial WP3 of the BETTER-B programme testing a pharmacological intervention (the use of mirtazapine to manage breathlessness), the EAB advised caution in promoting this aspect, when a clear evidence-base has not been established.

### Considerations due to COVID-19

The EAB offered advice on changes which may need to be made to adapt the BETTER-B programme to operate successfully within the limitations imposed by COVID-19. The EAB were supportive of the BETTER-B team identifying approaches to conduct the main trial (WP3) virtually, including conducting consent, questionnaires

#### 3.1.1 Question of unblinding at end of trial treatment or end of trial

The EAB were required to input on implementation of non-emergency unblinding for those who complete the trial or those who withdraw early while avoiding bias and ensuring the scientific integrity of the trial. CTRU

#### 2.1.2.1 Actions taken

EAB members have shared a letter of support towards continuation of the BETTER-B programme. This letter was included as evidence in the European Commission report due in Feb 2022.

**Conclusions:** EABs can provide useful support to research studies, ensuring they are scientifically robust and ethically sound. As innovations and medicine repursuing continue, EABs can add value that is timely and suited to the context.

BETTER-B website: [www.betterbreathe.eu](http://www.betterbreathe.eu)