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LETTER TO THE EDITOR

Reply: Overstating harms can have consequences

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We acknowledge Dr. Bedlack's concerns[1] and appreciate the opportunity to provide more clarity around the important issues he raises.

Our concern is not with expanded access programs (EAPs) per se, but rather with how these are currently operationalized. This includes the limited evidentiary basis for potential drug efficacy, and the opportunity cost of investing necessarily limited federal funds in such programs rather than in the sort of scientific research that is more likely to advance therapy development efforts.

The EAP programs funded to date have indeed been predicated upon results from trials whose design carried a very high risk of false positive discovery. The putative benefits have routinely

been based on post hoc analyses of only a selection of the many pre-specified analyses, without adjustment for multiplicity. Nonetheless, media communications have consistently made optimistic claims that are not subject to the essential critical appraisal of independent peer review. Moreover, the funded EAP's oft-stated goal of acquiring real world evidence of safety and efficacy seems disingenuous, given the uninformative results that have come from similarly sized randomized controlled trials.

While we recognize and value the hope that our patients derive from research participation and access to experimental agents, we assert that hope is false when it is based on information about the potential promise of a particular drug or EAP program that is not supported by the scientific evidence. We do, however, share Dr Bedlack's strong sense of hope, indeed expectation, that this is an unprecedented time in ALS research – one in which drugs with clinically meaningful benefit have the best ever chance to be developed. Part of the essential preparation for this new era is to acknowledge that the old systems for testing these candidates has not been working and needs to change.

Data availability

Data availability is not applicable to this article as no new data were created or analyzed in this study

Competing interests

MB reports consulting fees from Alector, Alexion, Annexon, Arrowhead, Biogen, Cartesian, Denali, Eli Lilly, Horizon, Immunovant, Novartis, Roche, Sanofi, Takeda, UCB, and uniQure. The University of Miami has licensed intellectual property to Biogen to support design of the ATLAS study. CJM reports consulting fees from Novartis, Biogen, Verge, PTC Therapeutics, Amylyx, Ferrer. MRT reports: grant funding from the UK National Institute for Health & Care Research, MND Association, LifeArc, and Target ALS; book royalties from Oxford University Press, Oneworld, and Karger; and ad hoc paid consultancies for Biogen, Novartis, uniQure and Aviadobio. RvE reports no conflicts.

Reference

1 Bedlack, RS. Overstating harms can have consequences. *Brain*. 2025.