Dear Reviewers,

Many thanks for taking the time to consider our paper and provide feedback. On behalf of all authors, please find our responses and amendments below.

Yours Sincerely,

Doñah Sabbagh.

ID: 00646537

Our apologies for the incorrect prisma diagram – we have now corrected this. In response to the 2016 Cochrane review you mentioned, we included the following:

"Intravenous infusion of AAT from pooled human plasma is a direct and efficient method for increasing plasma AAT levels, and can reduce progression of emphysema in AATD. Controversially, a recent Cochrane review suggests there is insufficient evidence supporting the efficacy of IV AAT in emphysema and lung disease. This conclusion may be due to the difficulty in assessing success in AATD lung pathology – progression of disease is best confirmed with CT imaging, which is currently only used in a research setting. In contrast, the response of panniculitis to augmentation therapy is easy to assess clinically." [Discussion]

ID: 00646516

Thank you for your comments. We have subsequently included the following paragraph about steroids/steroid-sparing agents:

"There is no apparent cause for the failure of steroids or steroid-sparing agents in AATD-panniculitis. Perhaps the mechanism of AATD does not facilitate the action of immunosuppressants, or there is a narrow therapeutic window. This could be explored by stratification of patients by dose and route of administration. Further understanding of this may unlock better comprehension of AATD." [Discussion]

ID: 00646519

The inheritance pattern of AATD was described in the original document, but as a result of your comments we have moved this to a more obvious location (as follows):

"AATD is a rare, autosomal co-dominant genetic disorder that increases the risk of emphysema…" [Introduction]

Thanks to your comments, we realised the original manuscript had been misleading about the genotypes included for review – only PIZZ genotypes were chosen for inclusion, as absolute confirmation of the diagnosis (and cause of the presenting panniculitis). We have amended the methods section, and included the following paragraph in response to your comments:

"As a result, the evolution of disease in each patient was not documented to a degree allowing comparison or commentary. Furthermore, as only PIZZ genotypes were included, it is not possible to assess whether different genotypes respond better to different treatments." [Discussion]