**Things to discuss.**

**MAJOR**

1. How to include hospitalization and death data
2. Rechanging definition of serious and non-serious drug reactions
   1. Need to define hosp & A&E as serious and GP as non DONE
   2. Separately report on AE-> hospitalization
   3. Rename drug reactions – hosp vs non
3. Include only those with positive test – matched control cohort
   1. Accept loss of power
   2. Sensitivity analysis with those without test
4. Start date
   1. from positive test for everyone
   2. from positive test control and treatment for treatment

**From Linda**

Approaches to mitigate the biases in your study (immortal time bias, non-positivity, misaligned time zero, residual confounding, unclear estimand):

1. Start follow-up at date of positive test in both groups. Exclude treated but ineligible according to EHR data from your study population, accepting a loss of power by improving the design of the study: introducing comparable groups with an aligned time zero & mitigating immortal time bias.
   1. done
2. Starting follow-up at positive test introduces a time-varying exposure (using future information to stratify study pop into treated vs untreated will introduce immortal time bias again, see more details below)
   1. done
3. For the Paxlovid comparison, exclude people who are ineligible for Paxlovid from your study population (solving the non-positivity in your study). Chris Wood has helped us to construct a codelist for absolute Paxlovid contraindications, see: [https://www.opencodelists.org/codelist/opensafely/paxlovid-nirmatrelvirritonavir-absolute-contraindications-dmd/774852b7/](https://eur03.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.opencodelists.org%2Fcodelist%2Fopensafely%2Fpaxlovid-nirmatrelvirritonavir-absolute-contraindications-dmd%2F774852b7&data=05%7C01%7Ckatie.bechman%40kcl.ac.uk%7Cc4086b051f3e46816d0f08dbd18dba61%7C8370cf1416f34c16b83c724071654356%7C0%7C0%7C638334178893176607%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C3000%7C%7C%7C&sdata=26sKggmzluA9h3jyysVl6eABhchW%2FgC4LfdJ%2FDeBoFQ%3D&reserved=0).
   1. done
4. You might want to include information on e.g. care home / dementia as covariates (I believe quite a strong predictor for molnupiravir treatment, and arguably a confounder of your exposure – outcome association? But leave this open to clinical experts :-));
   1. done
5. consider using region io STP in your models to improve stability if STP is too granular (based on my own experience – this might not be the case in your study pop as long follow-up!).
   1. done

As per point 2 above, we have to find a way to ‘deal’ with the time-varying exposure in your study. IMO there are two approaches you can take, and it really depends on the aim of your study which route fits your purpose best:

* Option 1 is the **‘causal route’**, which entails designing a target trial & explicitly defining the causal estimand. For example, if your objective is “to estimate the risk of AEs within 28 days associated with use of x versus no-treatment in non-hospitalised high-risk COVID-19 patients” you can apply the sequential trial approach to estimate the observational analogue of a intention-to-treat or per-protocol effect. You can find the protocol of the Paxlovid study describing this approach here: [https://docs.google.com/document/d/1vjyUWNTBcN6c1aYDQxl8UPsXzkvV-RoREc2GflLXIB8/edit](https://eur03.safelinks.protection.outlook.com/?url=https%3A%2F%2Fdocs.google.com%2Fdocument%2Fd%2F1vjyUWNTBcN6c1aYDQxl8UPsXzkvV-RoREc2GflLXIB8%2Fedit&data=05%7C01%7Ckatie.bechman%40kcl.ac.uk%7Cc4086b051f3e46816d0f08dbd18dba61%7C8370cf1416f34c16b83c724071654356%7C0%7C0%7C638334178893176607%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C3000%7C%7C%7C&sdata=TbuEexgg%2FbFb%2BXWomq4Ea68PetqEGe2XKXcHR6YPuXU%3D&reserved=0). The code of the ITT analysis is available on GH and the per-protocol analysis is under development: [https://github.com/opensafely/pax-non-users](https://eur03.safelinks.protection.outlook.com/?url=https%3A%2F%2Fgithub.com%2Fopensafely%2Fpax-non-users&data=05%7C01%7Ckatie.bechman%40kcl.ac.uk%7Cc4086b051f3e46816d0f08dbd18dba61%7C8370cf1416f34c16b83c724071654356%7C0%7C0%7C638334178893176607%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C3000%7C%7C%7C&sdata=qTq0Vws8tgBbe6C0qMWkhVBLisqjs%2FHZK5hDTc9kYpI%3D&reserved=0) (I’m happy to walk you through the repo!)
* Option 2 is the ‘**descriptive/exploratory route’**, which entails using a time-varying Cox model to model the time-varying exposure. @Bang.Zheng has used this approach in his UKRR analysis and has Stata code for doing so. You can find his paper here: [https://academic.oup.com/ckj/advance-article/doi/10.1093/ckj/sfad184/7240159](https://eur03.safelinks.protection.outlook.com/?url=https%3A%2F%2Facademic.oup.com%2Fckj%2Fadvance-article%2Fdoi%2F10.1093%2Fckj%2Fsfad184%2F7240159&data=05%7C01%7Ckatie.bechman%40kcl.ac.uk%7Cc4086b051f3e46816d0f08dbd18dba61%7C8370cf1416f34c16b83c724071654356%7C0%7C0%7C638334178893176607%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C3000%7C%7C%7C&sdata=ME3Xz6rpzZqsBAEKFzFZkI9ym8aFne4sfFyWiQaMrHQ%3D&reserved=0) and I’m sure he’s happy to explain in more detail if helpful! I’ve named this ‘descriptive/exploratory’ because it is unclear to me what the causal estimand is if you were to take this approach (designing a target trial makes this explicit and easy) – but people brighter than me can maybe help here!

**ANALYSIS JOB**

1. Start date
   1. Start follow-up at date of positive test in both groups- done
   2. from positive test control and treatment for treatment - done
2. Exclude treated but ineligible according to EHR data from your study population - done
   1. Sensitivity with all - done
3. Change study end date – done
   1. last date of treatment 26/6 last positive text 26/6
4. Create serious and non serious done
5. Fix flow sheet done
6. Schoenfeld residuals – graphs done
7. Describe when AEs occurred
8. Number in treatment arm with covid test <5 days before treatment and median time between post test and treatment done
9. Check median age histogram
10. Calculate variance in propensity model
11. Changed immunodef to include immunosuppression - ? not included on blueteq?

Industry £250K

Molecure - OATD Chitinase (Galapagos)

Mirroring

Epi sarcoid UK

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CPRD £20K

James / mine time

Clinician fellow time

NIHR

independent

Note