Monitoring and signal detection activities for ADR reports concerning the COVID 19 vaccine – December 2021

- Updated in December 2021 to acknowledge the announcement from JCVI that those aged 18 to 39 will also be eligible for a booster when the NHS calls them forward.
- The following sets out the updated process effective from 9th December 2021 for rapid, data retrieval and distribution and signal assessment and management.

ADR Report Processing

- The use of the AI tool will help us by reducing the amount of manual coding for each report, thereby saving resource in processing cases and ensuring they are rapidly available for scientific analysis. The AI tool was implemented from the 14th December 2020.

- Further steps have now been introduced to ensure rapid case processing as the volume of reports has increased greatly. ADR reports are now auto committed to the database and VIRG have a robust review process now in place to identify and reclassify any reports that require manual intervention. Additionally, MedDRA has now been mandated on the website.

- Any reports reviewed during signal detection whereby coding is identified to be incorrect, should be moved to the reclassification step or added to the reclassification spreadsheet and updated through the compliance allocation as soon as possible.

Signal Detection

- The substances concerning the different COVID 19 vaccines in use in the UK, TOZINAMERAN (Comirnaty, Pfizer), CHADOX1 NCOV 19 (Vaxzevria, Astra Zeneca) and MRNA 1273 (Spikevax, Moderna) should be allocated in Empirica to the lead assessor for each vaccine.

- Signal comments should be added to all vaccine event combination in Empirica by 2pm on Friday each week by the vaccine assessor assigned with this task.

- The Signal Management Team will extract all committed case reports received from all sources in relation to the COVID 19 vaccine(s) for review, including data mining outputs which will be circulated to the product assessment teams and allocated as appropriate. These are also stored on SharePoint.

- The Signal Management Team will provide the Pharmacoepidemiology team with all reports concerning AESI to conduct the observed vs expected analyses. Individual line listings to include patient age, the event and the date it started, dose information and date of vaccination(s), brand of vaccine.

New vaccines during the first weeks of deployment

- It is the responsibility of the lead assessor (or deputy) to allocate available data to their team as appropriate.

- Data outputs as above will be circulated to the vaccine product team Monday Friday by the Signal Management team.

- Assessors are responsible for deciding whether the report requires follow up and this should focus on reports containing AESIs and fatal reports. If the report requires specific follow up for further information, then the presenting assessor is responsible for ensuring this follow up is completed.

- ***Data in Under 18s:*** The Signal Management team will provide bi weekly line listings of ADR reports received concerning under 18s or patients with a neonate, infant, child or adolescent age group from w/c 20th September. These will be provided on a Tuesday and Friday, containing all paediatric reports at each DLP as well as the number of reports received between DLPs in a separate tab.

- The frequencies of these outputs will be reviewed as the roll out in under 18's progresses. A list of Adverse events of Special Interest (AESI) for the under 18 year age group can be found in the refined PV strategy document, and cases reporting these terms should have particular focus for signal assessment and requesting follow up. This list may be adapted according following any updates to the UK vaccine programme. Consideration should also be given to any cases reporting co administration with another vaccine e.g. nasal flu vaccine. Medical assessor input on signal detection should be sought where appropriate, and paediatric medical assessor advice will be available at the signal meetings. Any concerns relating to safety issues within this population should be raised at the next available signal detection meeting, where the first half of the meeting will be dedicated to discussing paediatric data. Requests for follow up information and reclassifications, including where inaccurate ages are reported, should be made in the usual documents.

- ***Booster Data****:* Booster cases can be identified using the "additional dose information" field. The following key can be used to identify the schedules provided in this field:

Front end text provided to the reporter	***Mapped in xml/sentinel case folder***
Dose one	*Dose 1*
Dose two	*Dose 2*
Booster same brand as primary vaccines	*Dose 3a*
Booster different brand to primary vaccines	*Dose 3b*
Booster other/unknown brand	*Dose 3c*

Assessment of booster cases should take into account the AESI identified as particular concern for boosters (please see updated PV strategy document), any reports with co administration of another vaccine or recent administration of another vaccine (eg. seasonal flu or shingles vaccination), mixed

or homologous dosing schedules and use of half dose Moderna (including risk of infection from multiple bung piercings). Any concerns relating to safety issues with boosters should be raised at the next available signal detection meeting. Requests for follow up information and reclassifications, including where inaccurate classifications of boosters are reported, should be made in the usual documents.

To note, there will also be active surveillance underway for the flu vaccine, including co administration of COVID 19 vaccines (boosters or otherwise), and data from this monitoring can also be fed into the signal meeting.

Established process after initial deployment

Pfizer/BioNTech Vaccine (Comirnaty, TOZINAMERAN)

AstraZeneca/Oxford Vaccine (Vaxzevria)

Moderna Vaccine (Spikevax)

- The Empirica standard signal management run will be reviewed by the designated vaccine assessor every Monday. This will include all reports committed in the previous week (Mon Fri). The Lead and/or Deputy Lead assessors will be responsible for ensuring a 'wider picture' trend analysis and review of the Empirica Signal data on with the input of a medical assessor where necessary is performed.

- If the Lead/Deputy Lead assessor identifies any trend/vaccine event combination/areas of interest, requiring further investigation, these should be raised immediately, at the next Signal Meeting where appropriate, or be allocated by the Lead/Deputy Lead for review by a member of the vaccine team depending on the urgency of the matter.

- As of 9th December 2021, the Signal Management Team will be responsible for providing the Lead and Deputy Lead assessors with a booster output in Excel format on Tuesdays, Thursdays and Fridays. The Excel file will include a line listing of all booster reports received for the vaccine to date; a line listing of all booster reports received for the signal run period as well as an output from the Empirica data mining run which provides a summary of the booster drug event combinations reported for the signal period, the total number of booster reports of the drug event combination in the database together with the corresponding 'Vaccine' EB05 (which is generated on a background of COVID 19 vaccine cases only). The Tuesday data will include all booster reports committed on the preceding Friday, Saturday, Sunday and Monday. The Thursday output will contain those committed on Tuesday and Wednesday, and the Friday output will include all reports committed on the previous day. The output provided on a Wednesday will include all cases (regardless of dose) received over the previous week. Please refer to Annex 4 for details of the weekly data outputs as of 9th December 2021.

- Using these data outputs, the Lead and/or Deputy Lead assessors will be responsible for daily triage of reports with particular focus on fatal reports and AESIs.

- If the Lead/Deputy Lead assessor identifies any vaccine event combination/areas of interest requiring further investigation, these should be raised immediately, or at the signal meeting on Tuesday/Thursday or be allocated by the Lead/Deputy Lead for review by a member of the vaccine team depending on urgency of the matter.

- The Lead/Deputy Lead is responsible for ensuring that details of all fatal cases and AESIs requiring follow up are added to the relevant spreadsheet on Share Point for follow up.

- The Lead/Deputy Lead is responsible for ensuring that details of reports of vaccine use during pregnancy and breast feeding are forwarded to the relevant contact within the MHRA.

- The Lead/Deputy Lead is responsible for ensuring that details of reports of vaccine quality issues or administration issues are highlighted to the relevant MHRA contact.

COVID 19 Vaccine Signal Detection Meeting

- COVID 19 vaccine signal detection meetings will be conducted at 4pm every Tuesday and Thursday.

- Attendees will include designated assessors from VIRG and BRMG see list in Annex 1. The list of attendees is subject to change depending on the need for expertise in certain areas and the number of reports available for assessment.

- The Pharmacoepidemiology team will report back to the group on their analysis conducted for AESIs or particular issues of interest on a regular basis.

- Any signals requiring further action should go to the Signal Management Review Meeting (SMRM), however should a signal require urgent action, ad hoc meetings will be scheduled to decide next steps as appropriate.

- Note that for any safety signals for which lab testing would be valuable, we are able to reach out to Nicola Rose (Head of Virology at NIBSC).

- Minutes will be collected and shared after each meeting by VIRG CVSD assessors. Minutes will also be stored on SharePoint.

Annex 1 – COVID 19 Vaccine Signal Meeting Attendees

COVID 19 Vaccine Signal Meeting Attendees	
Sarah Branch	
VIRG	**BRMG**
	Catherine Tregunno
Lilly Wells	Katherine Donegan
Phil Tregunno	Angeliki Siapkara
	Patrick Batty
	(AZ Lead)
	(Moderna Lead)
Any other relevant VIRG signal assessors	Shiva Ramroop
	Julie Beynon

	Fazil Afzal

Annex 2 Helpful SharePoint Links

- Assessor daytime and out of hours rota: https://mhra.sharepoint.com/:f:/r/teams/t14/ts2/ts3/cd/Covid 19%20vigilance/COVID 19%20Vaccine/Assessor%20daytime%20and%20out%20of%20hours%20rota?csf=1&web=1&e=60aQiH
- Templates for follow up: https://mhra.sharepoint.com/:f:/r/teams/t14/ts2/ts3/cd/Covid 19%20vigilance/COVID 19%20Vaccine/Follow%20Up?csf=1&web=1&e=OhA5nL
- AZ Vaccine Daily Case Outputs: https://mhra.sharepoint.com/:f:/r/teams/t14/ts2/ts3/cd/Covid 19%20vigilance/COVID 19%20Vaccine/COVID 19%20Vaccine%20ASTRAZENECA%20Case%20Outputs?csf=1&web=1&e=VJ5YKm
- Pfizer Vaccine Daily Case Outputs: https://mhra.sharepoint.com/:f:/r/teams/t14/ts2/ts3/cd/Covid 19%20vigilance/COVID 19%20Vaccine/COVID 19%20mRNA%20BioNTech%20Case%20Outputs?csf=1&web=1&e=lK2TMy
- Moderna Vaccine Daily Case Outputs: https://mhra.sharepoint.com/:f:/r/teams/t14/ts2/ts3/cd/Covid 19%20vigilance/COVID 19%20Vaccine/COVID 19%20VACCINE%20MODERNA%20Case%20Outputs?csf=1&web=1&e=Rdbf0S
- Daily Signal Meeting Minutes: https://mhra.sharepoint.com/:f:/r/teams/t14/ts2/ts3/cd/Covid 19%20vigilance/COVID 19%20Vaccine/Signal%20Meeting%20Minutes?csf=1&web=1&e=qWgYlG
- Uptake Data: https://mhra.sharepoint.com/:f:/r/teams/t14/ts2/ts3/cd/Covid 19%20vigilance/COVID 19%20Vaccine/Uptake%20data?csf=1&web=1&e=GH4q2z
- MHRA Core RMP: https://mhra.sharepoint.com/:b:/r/teams/t14/ts2/ts3/cd/Covid 19%20vigilance/COVID 19%20Vaccine/MHRA%20Guidance%20on%20PhV.RMP%20for%20COVID%2019%20vaccines%20(final).pdf?csf=1&web=1&e=4Kdhfz
- Pfizer Vaccine RMP: https://mhra.sharepoint.com/:f:/r/teams/t14/ts2/ts3/cd/Covid 19%20vigilance/COVID 19%20Vaccine/Pfizer%20RMP?csf=1&web=1&e=PQnU0y
- AZ Vaccine RMP: https://mhra.sharepoint.com/:f:/r/teams/t14/ts2/ts3/cd/Covid 19%20vigilance/COVID 19%20Vaccine/AZ%20RMP?csf=1&web=1&e=qV6DxE)
- Moderna Vaccine RMP: https://mhra.sharepoint.com/:f:/r/teams/t14/ts2/ts3/cd/Covid 19%20vigilance/COVID 19%20Vaccine/Moderna%20RMP?csf=1&web=1&e=T3FSDi
- List of current issues/issues being reviewed: https://mhra.sharepoint.com/:x:/r/teams/t14/ts2/ts3/cd/Covid 19%20vigilance/COVID 19%20Vaccine/Signal%20Meeting%20Minutes/Log%20of%20covid 19%20vaccine%20issues%20discussed%20at%20meetings.xlsx?d=wb12776446aac4dd19305a744dec75cab&csf=1&web=1&e=lfvBJ1
- AESI Pfizer Vaccine Line Listing of cases received by MHRA for Epi Team: https://mhra.sharepoint.com/:x:/r/teams/t14/ts2/ts3/cd/Covid 19%20vigilance/COVID 19%20Vaccine/AESI%20Line%20Listing.xlsx?d=w081f7a68b6954821b0a7d9dd3921f15d&csf=1&web=1&e=f6rrOx
- Refined PV strategy document: PV strategy document

Annex 3 – Frequently Asked Questions

1. **What should I present to the daily COVID 19 Vaccine Signal Detection meeting?**
   Due to the large volume of reports being received and reviewed, presentations should be as brief as possible. Reports/signals should only be presented if they constitute a safety concern, are an Adverse Event of Special Interest (AESI) or concern a fatal case. There is no need to go into case details unless a specific question to the meeting is posed. ADR reports do not need to be presented just for information/interest. Assessors should take in to account the large uptake of the vaccine when considering whether to present a Vaccine Event Combination.

2. **What is the difference between the EB05 vaccine and EB05 combined?**
   The two runs will flag up different things as signals. The vaccine only background will suppress a lot of the typical local reactions seen with vaccines such as injection site reactions so a signal for these in the vaccine background will indicate an excess for this vaccine over other vaccines in our dataset. The combined background (drugs and vaccines) will likely signal strongly for local reactions as the majority of our reports are for oral medications. The advantage of having the combined background run is to detect signals for serious ADRs such as Guillain Barre Syndrome that might be suppressed in the vaccine only background as this condition is typically reported for vaccines and not drugs.

3. **Why doesn't the daily Excel output contain hyperlinks to Sentinel/Empirica case folders?**
   Unfortunately, the daily line listings are extracted using Empirica and Empirica does not have the functionality to be able to produce downloadable hyperlinks that could be included in the daily Excel output.

4. **Why doesn't the Data Mining Results tab on Empirica show newly received cases alongside total cases?**
   Unfortunately this is another limitation of Empirica – only the total number of cases can be seen on the Data Mining Results tab. Suzie has kindly put together a programme which allows us to display the total number of new cases on the Data Mining Tab of the daily Excel output. New cases for each PT can be easily searched on the Excel sheet using the tab labelled with the date and filtering on the column entitled Reaction(s) + Outcome(s).

Annex 4 – Summary of COVID 19 Vaccine Data Outputs commencing 9th December 2021

<table>
<tr><th>Monday</th><th>Tuesday</th><th>Wednesday</th><th>Thursday</th><th>Friday</th></tr>
<tr><td rowspan="2">Weekly Empirica signal run</td><td>Paediatric output all vaccines</td><td rowspan="2">Output of all COVID 19 vaccines received the previous week (regardless of dose)</td><td></td><td>Paediatric output all vaccines</td></tr>
<tr><td>Daily booster output all vaccines</td><td>Daily booster output all vaccines</td><td>Daily booster output all vaccines</td></tr>
</table>