**Supplementary Material**

|  |  |
| --- | --- |
| **Inclusion Criteria** | 1. Clinical guidelines including recommendation(s) about clozapine treatment and monitoring requirements
2. Covering adult populations (18+) with a diagnosis of treatment-resistant psychosis, including schizophrenia, schizoaffective disorder, schizophreniform disorder and psychotic disorder
3. Published from 1956, when clozapine was synthesised,(Crilly, 2007) to the current date.
 |
| **Exclusion Criteria**  | 1. Non-specific worldwide or continental guidelines
2. Only contained recommendations about non-pharmacological treatment for schizophrenia
3. Conference abstracts, commentary, or other opinion pieces not made systematically based on evidence.
 |
| **Search Terms**  | Treatment\*resistant psychosis\* OR Treatment\*refractory psychosis\* OR Treatment\*resistant schizophrenia OR Treatment\*refractory schizophrenia OR clozapine AND algorithm OR guide\* OR implementation OR monitor\* protocol\*. No language restriction was applied to the search strategy. Non-English guidelines were translated using Google Translator. |

Table 1. Literature Search

**Search strategies for Embase, Medline, PsychInfo and PubMed databases.**

|  |
| --- |
| **Embase** |
| 1 | Treatment\*resistant psychosis\*.mp. OR Treatment\*refractory psychosis\*.mp. OR Treatment\*resistant schizophrenia.mp. OR Treatment\*refractory schizophrenia.mp. OR clozapine.mp. |
| 2 | algorithm.mp. OR guide\*.mp. OR implement\*.mp. OR monitor\*.mp. OR protocol.mp. |
| 3 | 1 AND 2  |
| **Medline** |
| 1 | Treatment\*resistant psychosis\*.mp. OR Treatment\*refractory psychosis\*.mp. OR Treatment\*resistant schizophrenia.mp. OR Treatment\*refractory schizophrenia.mp. OR clozapine.mp. |
| 2 | algorithm.mp. OR guide\*.mp. OR implement\*.mp. OR monitor\*.mp. OR protocol.mp. |
| 3 | 1 AND 2  |
| 4 | limit 5 to (yr="1956 -Current") |
| **PsychInfo** |
| **1** | Treatment\*resistant psychosis\*.mp. OR Treatment\*refractory psychosis\*.mp. OR Treatment\*resistant schizophrenia.mp. OR Treatment\*refractory schizophrenia.mp. OR clozapine.mp. |
| **2** | algorithm.mp. OR guide\*.mp. OR implement\*.mp. OR monitor\*.mp. OR protocol.mp. |
| **3** | 1 AND 2  |
| **4** | limit 5 to (yr="1956 -Current") |
| **PubMed** |
| ("algorithm"[MeSH Terms] OR "algorithm"[All Fields] OR " guide\*"[All Fields] OR ("guide\*"[MeSH Terms] OR "implement\*"[MeSH Terms] OR "implement\*"[All Fields] OR "monitor\*"[MeSH Terms] OR "monitor\*"[All Fields] OR "protocol"[MeSH Terms] OR "protocol"[All Fields]AND ("Schizophrenia Spectrum and Other Psychotic Disorders"[MeSH Terms] OR "psychosis"[Text Word] OR "schizophrenia\*"[Text Word] OR "schizophreniform\*"[Text Word] OR "schizoaffective\*"[Text Word] OR "psychotic\*"[Text Word] OR "schizophrenic\*"[Text Word] OR "treatment-resistant schizophrenia"[All Fields] OR "treatment-resistant psychosis"[All Fields]) |

**Supplementary Material 2:**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Countries**  | **Mandatory monitoring (i.e. no blood no drug)** | **Haematological Monitoring Details** | **Criteria for Clozapine Discontinuation (****mm3/L)** | **Clozapine Rechallenge Restrictions** | **Source** |
|  | **WCC** | **ANC** | **Frequency (Duration in weeks)** | **Other parameters** | **Adjusted BEN Criteria** | **WCC** | **ANC** |
| Weekly | Fortnightly | Monthly |
| ***Africa***  |  |  |  |  |  |  |  |  |  |  |  |  |
| Algeria  | ✗**g** | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗**b** |
| Cameroon | ✗**g** | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ |
| Egypt  | ✗ | ✓ | ✓ | ✗**i** | ✗ | ✗ | ✗ | ✗ | <3·0 | <1·5 | ✗ | ✗**b** |
| Ethiopia  | ✗**g** | ✓ | ✓ | ✓ (18) | ✓ (19-51) | ✓ (>52) | ✗ | ✗ | <3·0 | <1·5 | ✗ | NG |
| Gabon | ✗**g** | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ |
| Ghana  | ✗ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ |
| Guinea | ✗**g** | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ |
| Ivory Coast  | ✗**g** | ✓ | ✓ | ✗ **i** | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ |
| Kenya  | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗**b** |
| Libya | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ |
| Malawi | ✗**g** | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ |
| Nigeria  | ✗ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗**b** |
| Somalia  | ✗ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗**b** |
| South Africa | ✗ | ✗ | ✓ | ✗ | ✗ | ✗ | ✗ | ✓ | ✗ | <1·0 | ✗ | ✗**b** |
| Sudan | ✗ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ |
| Tanzania  | ✗**g** | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ |
| Tunisia  | ✗ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗**b** |
| Uganda  | ✗**g** | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗**b** |
| Zambia | ✗**g** | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ | <3·0 | <1·5 | ✗ | NG |
| Zimbabwe  | ✗**g** | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗**b** |
| ***Asia*** |  |  |  |  |  |  |  |  |  |  |  |  |
| Armenia | ✗ | ✓ | ✓ | ✓ (26) | ✓ (27-52) | ✓ (>52) | ✗ | ✗ | <4·0 | ✗ | ✗ | ✗ |
| Bangladesh | ✗ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗**b** |
| Bhutan | ✗**g** | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗**b** |
| Cambodia | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗**b** |
| China  | ✗ | ✓ | ✓ | ✓ (24) | ✓ (>24) | ✓(>24)**e** | ✗ | ✗ | <2·0 | <1·0 | ✗ | NG |
| Hong Kong  | ✓ | ✓ | ✓ | ✓ (18) | ✗ | ✓ (>19) | ✗ | ✗ | <3·0 | <1·5 | ✗ | RR |
| India  | ✗ | ✓ | ✓ | ✗ | ✗ | ✗**c** | ✗ | ✗ | ✗ | ✗ | ✗ | RR |
| Iran | ✗ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ | <3·5 | <1·5 | ✗ | ✗**b** |
| Israel  | ✓ | ✗ | ✓ | ✓ (18) | ✗ | ✓ (>19) | ✓ | ✓ | ✗ | <1·0 | ✗ | NG |
| Japan\* | ✓ | ✓ | ✓ | ✓ (24) | ✓ (>24) | ✗ | ✓ | ✗ | <3·0 | <1·5 | ✓  | NG |
| Jordan  | ✗ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ |
| Lebanon  | ✗ | ✗ | ✓ | ✓ (18) | ✓ (19-51) | ✓ (>52) | ✗ | ✗ | ✗ | <1·0 | ✗ | SmPC |
| Malaysia | ✓ | ✓ | ✓ | ✓ (18) | ✗ | ✓ (>19) | ✗ | ✗ | <3·0 then <2·5α | <1·5 then <1·0α | ✓ | NG |
| Nepal  | ✗ | ✓**f** | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗  | ✗**b** |
| North Korea | ✗ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗**b** |
| Oman  | ✗ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗**b** |
| Qatar  | ✗ | ✓ | ✓ | ✓ (18) | ✓ (19-51) | ✓ (>52) | ✗ | ✓ | <3·0 | <1·5 | ✓ (Haematologist consultation) | NG |
| Saudi Arabia  | ✓ | ✓ | ✓ | ✓ (18) | ✗ | ✓ (>19) | ✓ | ✗ | <3·0 then <2·5α | <1·5 then <1·0α | ✓ | NG |
| Singapore  | ✓ | ✓ | ✓ | ✓ (18) | ✗ | ✓ (>19) | ✗ | ✗ | <3·0 then <2·5α | <1·5 then <1·0α | ✓ (Index ANC limit) | RR |
| South Korea  | X | ✓ | ✓ | ✓ (18) | ✗ | ✓ (>19) | ✗ | ✗ | <3·0 then <2·5α | <1·5 then <1·0α | ✓  | NG |
| Sri Lanka | X | ✓ | ✓ | ✓ (18) | ✓ (19-51) | ✓ (>52) | ✗ | ✗ | ✗ | ✗ | ✗ | ✗**b** |
| Taiwan | X | ✓  | ✓  | ✓ (18) | ✗ | ✓ (>19) | ✗ | ✗ | <1·0 | <0·5 | ✗ | NG |
| Thailand | ✗ | ✓  | ✓  | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | NG |
| Yemen | ✗ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗**b** |
| ***Europe*** |  |  |  |  |  |  |  |  |  |  |  |  |
| Albania  | ✗**f** | ✓ | ✓ | ✗ **i** | ✗ | ✗ | ✗ | ✗ | <3·0 | <1·5 | ✓ | SmPC |
| Austria  | ✓ | ✓ | ✓ | ✓ (18) | ✗ | ✓ (>19) | ✗ | ✗ | <3·0 | <1·5 | ✓ | SmPC |
| Azerbaijan | ✓ **f** | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ | <3·0 | <1·5 | ✓ | NG |
| Belgium | ✓ | ✓ | ✓ | ✓ (18) | ✗ | ✓ (>19) | ✗ | ✗ | <3·0 | <1·5 | ✓  | SmPC |
| Bulgaria | ✗ | ✓ | ✓ | ✓ (4) | ✗ | ✓ (>4) | ✗ | ✗ | ✗ | ✗ | ✓ | NG |
| Croatia  | ✓ | ✓ | ✓ | ✓ (18) | ✗ | ✓ (>19) | ✗ | ✗ | <3·0 | <1·5 | ✓  | SmPC |
| Cyprus  | ✓ | ✓ | ✓ | ✓ (18) | ✗ | ✓ (>19) | ✗ | ✗ | ✗ | ✗ | ✗ | ✗**b** |
| Czech Republic | ✓ | ✓ | ✓ | ✓ (18) | ✗ | ✓ (>19) | ✗ | ✗ | <3·0 then <2·5α | <1·5 then <1·0α | ✓  | NG |
| Denmark | ✓ | ✓ | ✓ | ✓ (18) | ✗ | ✓ (>19) | ✗ | ✗ | <3·0 | <1·5 | ✓ | SmPC |
| Estonia  | ✓  | ✓  | ✓ | ✓ (18) | ✗ | ✓ (>19) | ✗ | ✗ | <3·0 | <1·5 | ✓ | SmPC |
| Finland | ✗ | ✓ | ✓ | ✓ (18) | ✗ | ✓ (>19) | ✗ | ✗ | <3·0 then <2·5α | <1·5 then <1·0α | ✓ | SmPC |
| France  | ✓ | ✓ | ✓ | ✓ (18) | ✗ | ✓ (>19) | ✗ | ✗ | <3·0 | <1·5 | ✓ | SmPC |
| Germany  | ✓ | ✓ | ✓ | ✓ (18) | ✗ | ✓ (>19) | ✓ | ✗ | <3·0 | <1·5 | ✓ | SmPC |
| Greece  | ✓ | ✓ | ✓ | ✓ (18) | ✗ | ✓ (>19) | ✗ | ✗ | <3·0 | <1·5 | ✓ | SmPC |
| Hungary  | ✓ | ✓  | ✓  | ✓ (18) | ✗ | ✓ (>19) | ✗ | ✗ | <3·0 | <1·5 | ✓ | NG |
| Iceland | ✗ | ✓ | ✓ | ✓ (18) | ✗ | ✓ (>19)**d** | ✗ | ✓ | <3·0 | <1·5 | ✓  | SmPC |
| Ireland | ✓ | ✓ | ✓ | ✓ (18) | ✓ (19-51) | ✓ (>52) | ✗ | ✗ | <3·0 | <1·5 | ✓  | NG |
| Italy | ✓ | ✓ | ✓ | ✓ (18) | ✗ | ✓ (>19) | ✗ | ✗ | <3·0 | <1·5 | ✓  | SmPC |
| Latvia  | ✓ | ✓ | ✓ | ✓ (18) | ✗ | ✓ (>19) | ✗ | ✗ | <3·0 | <1·5 | ✓ | SmPC |
| Lithuania | ✓ | ✓ | ✓ | ✓ (18) | ✗ | ✓ (>19) | ✗ | ✗ | <3·0 | <1·5 | ✓ | NG |
| Luxembourg  | ✓ | ✓ | ✓ | ✓ (18) | ✗ | ✓ (>19) | ✗ | ✗ | <3·0 | <1·5 | ✓ | SmPC |
| Malta  | ✓ | ✓ | ✓ | ✓ (18) | ✓ (19-51) | ✓ (>52) | ✗ | ✗ | <3·0 | <1·5 | ✓ | NG |
| Netherlands | ✓ | ✓ | ✓ | ✓ (18) | ✗ | ✓ (>19)**c** | ✗ | ✗ | <3·0 | <1·5 | ✓  | SmPC |
| Norway  | ✓ | ✓ | ✓ | ✓ (18) | ✗ | ✓ (>19) | ✗ | ✗ | <3·0 | <1·5 | ✓ | NG |
| Poland  | ✗ | ✓ | ✓ | ✓ (18) | ✗ | ✓ (>19) | ✗ | ✗ | <3·0 | <1·5 | ✓ | NG |
| Portugal  | ✗ | ✓  | ✓  | ✓ (18) | ✗ | ✓ (>19) | ✗ | ✗ | <3·0 | <1·5 | ✓ | NG |
| Romania | ✓ | ✓ | ✓ | ✓ (18) | ✗ | ✓ (>19) | ✗ | ✗ | <3·0 | <1·5 | ✓  | NG |
| Russia  | ✓ | ✓ | ✓ | ✓ (18) | ✗ | ✓ (>19) | ✗ | ✗ | <3·0 | <1·5 | ✓ | SmPC |
| Slovakia  | ✓ | ✓ | ✓ | ✓ (18) | ✗ | ✓ (>19) | ✗ | ✗ | <3·0 | <1·5 | ✓ | SmPC |
| Slovenia  | ✓ | ✓ | ✓ | ✓ (18) | ✗ | ✓ (>19) | ✗ | ✗ | <3·0 then <2·5α | <1·5 then <1·0α | ✓ | SmPC |
| Spain | ✗ | ✓ | ✓ | ✓ (18) | ✗ | ✓ (>19) | ✗ | ✗ | <3·0 | <1·5 | ✓ | NG |
| Sweden | ✓ | ✓ | ✓ | ✓ (18) | ✗ | ✓ (>19) | ✓ | ✗ | <3·0 | <1·5 | ✓ | NG |
| Switzerland | ✓ | ✓ | ✓ | ✓ (18) | ✗ | ✓ (>19) | ✗ | ✗ | <3·0 then <2·5α | <1·5 then <1·0α | ✓  | SmPC |
| Turkey | ✓ | ✓ | ✓ | ✓ (18) | ✗ | ✓ (>19) | ✗ | ✗ | <3·0 | <1·5 | ✓ (Index WCC & ANC limit) | NG |
| United Kingdom | ✓ | ✓ | ✓ | ✓ (18) | ✓ (19-51) | ✓ (>52) | ✗ | ✓ | <3·0 | <1·5 | ✓ (off-license agreement) | NG |
| ***North America***  |  |  |  |  |  |  |  |  |  |  |  |  |
| Barbados  | ✗ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗**b** |
| Canada  | ✓ | ✓ | ✓ | ✓ (26) | ✓ (27-52) | ✓ (>52) | ✗ | ✓ | <2·0 | <1·5 | ✓ (off-license agreement) | NG |
| Costa Rica | ✗ | ✓ | ✓ | ✓ (18) | ✗ | ✓ (>19) | ✗ | ✗ | <3·0 | <1·5 | ✗ | NG |
| El Salvador | ✗ | ✓ | ✓ | ✓ (18) | ✗ | ✓ (>19) | ✗ | ✗ | ✗ | <1·5 | ✓ | SmPC |
| Mexico | ✗ | ✓  | ✓  | ✓ (12) | ✗ | (>13-52)**c** | ✗ | ✗ | ✗  | ✗  | ✗  | NG |
| St Lucia | ✗ | ✓  | ✓  | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗**b** |
| United States  | ✓ | ✗ | ✓ | ✓ (26) | ✓ (27-52) | ✓ (>52) | ✗ | ✓ | ✗ | <1·0 | ✗ | NG |
| ***Oceania and Australia*** |  |  |  |  |  |  |  |  |  |  |  |  |
| Australia  | ✓ | ✓ | ✓ | ✓ (18) | ✗ | ✓ (>19) | ✓ | ✗ | <3·0 | <1·5 | ✓ (off-license agreement) | RR |
| Fiji | ✓**f** | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✓ | ✗**b** |
| New Zealand | ✓ | ✓ | ✓ | ✓ (18) | ✗ | ✓ (>19) | ✗ | ✗ | <3·0 | <1·5 | ✓  | NG |
| Papua New Guinea | ✗**g** | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ |
| Tonga | ✗**g** | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ |
| ***South America*** |  |  |  |  |  |  |  |  |  |  |  |  |
| Argentina  | 4 | ✓ | ✓ | ✓ (18) | ✗ | ✓ (>19) | ✗ | ✗ | <3·0 | <1·5 | ✓ (Index ANC/WCC limit and timespan) | NG |
| Bolivia  | ✗**g** | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ |
| Brazil  | ✓ | ✓ | ✓ | ✓ (18) | ✗ | ✓ (>19) | ✗ | ✗ | <3·0 | <1·5 | ✓ (Haematologist consultation) | NG |
| Chile  | ✓ | ✗ | ✓ | ✓ (18) | ✗ | ✓ (>19) | ✗ | ✗ | ✗ | <1·0 | ✗ | NG |
| Colombia  | ✗ | ✓ | ✗ | ✓ (12) | ✗ | (>13-52)**c** | ✗ | ✗ | <3·5 | ✗ | ✗ | NG |
| Ecuador  | ✗ | ✓ | ✓ | ✓ (24) | ✓ (>24) | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | NG |
| Guyana  | ✗**g** | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ |
| Paraguay  | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ |
| Peru | ✗ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | <1·0 | ✓  | ✗**b** |
| Uruguay | ✗ | ✓  | ✓  | ✓ (18) | ✗ | ✓ (>19) | ✓ | ✗ | <3·0 | <1·5 | ✓ | NG |
| Venezuela | ✗ | ✓  | ✓  | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ |
| **Abbreviations** ANC: Absolute Neutrophil Count BEN: Benign Ethnic Neutropenia NG: National Guidelines NG: National Guidelines RR: Regional Guidelines SmPC: Summary of Product Characteristics UK: United Kingdom US: United States WCC: White Cell Counts \*Guidelines to be amended June 2021**Notes****α**After 18 weeks of treatment**b**US FDA REMS / UK MHRA / French HAS guidelines typically followed.**c**Where appropriate, routine monitoring can be ceased after 6 months of clozapine treatment (low frequency monitoring e.g. four times a year still recommended in the Netherlands, off-label). In the Netherlands, immediate WCC monitoring is also advised if any clinical suspicion of severe neutropenia. In Colombia and Mexico, monitoring two times a year is recommended after 12 months. **d**Often longer intervals in clinical practice **e**Optional**f**Typically every 6 months**g**Rarely used**h**Mandatory in public sector **i**Typically first 4 weeksCountries with known Non-Rechallenge Databases after a suspected clozapine-induced blood dyscrasia: Australia, Canada, United KingdomNational or sub-national guidelines on prescribing, stopping and restarting clozapine were categorised as either regulations or recommendations. Conditions in guidelines for prescribing, stopping and restarting clozapine that were mandatory were defined as “Regula-tions”. For example, in the UK blood monitoring is mandated by the marketing authorisation of clozapine. Non-mandatory conditions were defined as “Recommendations”. |

Table 2. Monitoring guidelines per country

**Supplementary Material 3: Stringency Index Indicators and Scoring**

***Delphi Survey Participants***

Using a 2-round modified Delphi methodology, a group of nineteen international experts were approached to identify indicators reflecting stringency of clozapine haematological monitoring guidelines. Experts were identified from i) publications on treatment-refractory psychosis and ii) Expertscape.(Expertscape, 2021) The selection criteria for invitation to the panel include being a specialist doctor or pharmacist in psychiatry. In addition, panel members must have had at least 3 years of clinical experience working within the chosen speciality. Finally, they must be fluent in English (due to the survey being completed in English).

***Identification of candidate stringency indices***

Prior to round 1 of the Delphi survey, a search of articles published up to 1st January 2021 examining guidelines for clozapine use on an internal scale was conducted using Ovid and PubMed. Potential indicators reflecting stringency of haematological monitoring guidelines were drawn from this literature search. In addition to the one study identified during the literature search (by

***Delphi Survey***

*Round one:*

For the first round of the Delphi survey, experts will be asked to score the importance of each item on a five-point Likert scale ranging from 1 (‘essential) to 5 (‘should not be included’). Panel members were able to suggest additional items. Items that were rated as ‘essential’ or ‘important’ by >80% of the panel were selected for inclusion. Items that were rated as ‘essential’ or ‘important’ by 50 – 79% of the panel entered round 2. Items that were rated as ‘essential’ or ‘important’ by <50% of the panel were discarded. These cut-off were chosen based upon previously published Delphi survey’s.(Petros et al., 2019) Participants were asked if there were other important haematological monitoring, discontinuation or rechallenge parameters that should be included such as discontinuation criteria based on platelet counts and eosinophil counts. The survey was distributed using Qualtrics software.

*Round two:*

For round two, panellists received lists of the ‘accepted’, ‘rejected’ and ‘to be re-rated’ items; for the latter, group medians and ranges were revealed and each participant's own Round 2 responses were provided, to enable comparisons with the group. New items suggested by the Round 1 panel were rated for the first time, only those considered ‘essential’ or ‘important’ by ≥80% of the sample were retained. Each indicator was rescaled by their maximum value to create a score between 0 and 100. These scores were then weighted to get the composite index, with higher scores indicating higher overall stringency.

*Ranking countries:*

Finally once consensus was reached, panellists were informed that each country would be given an overall stringency score depending on the according to the stringency of their clozapine regulations. Panellists were asked how each included indicator should contribute to the stringency index (total out of 100). In addition, each participant was asked whether countries with mandatory regulation guidelines (i.e. ‘no blood no drug’) should rank higher (i.e. stricter) than recommended guidelines. Specifically, panellists were asked whether the total score for countries with mandatory regulations should be weighted 1) no different, 2) by a factor of 1.5 3) by a factor of 2 or 4) by a factor of 3, compared to recommended guidelines.

***Pilot Survey***

A pilot survey was conducted with 10 specialist mental health pharmacists from the South London and Maudsley NHS Foundation Trust. Clinicians were asked to complete both rounds of the survey. The principle reason for the pilot was to establish the feasibility of the survey. There was a 100% response rate in round 1 and 2.

***Delphi Survey Results***

Nineteen clozapine experts participated in Round 1 (100% response rate) and 18 in Round 2 (95%). After two rounds of the survey, 7 indicators were endorsed by ≥80% of the panel based on their importance and on the consensus of the expert panel. The six indicators considered essential to include were 1) haematological monitoring parameters, 2) monitoring frequency, 3) ANC and 4) WCC thresholds for discontinuation, 5) rechallenge restrictions and 6) modified monitoring criteria for benign ethnic neutropenia. Suggested indicators considered not important to include were discontinuation criteria based on eosinophil and platelet counts. A detailed description of the calculation of the stringency index can be found below.

|  |  |
| --- | --- |
| **Variable** | **N = 19** |
| Gender  | Male(n= 17);Female(n=2) |
| Age | 35-44(n=2);45-54(n=5);55-64(n=7);65 and over(n=5) |
| Profession  | Doctor(n=17);Pharmacist(n=2) |
| Continents represented | Asia (n=1); Australia(n=2);Europe(n=16) |
| Experience (years) | 0-10(n=3);11-20(n=1 );21-30(n= 9);31 and above(n=6 ) |

**Table 3. Round 1 Participant Characteristics**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Monitoring parameter** | **Score**  | **Monitoring frequency in weeks (weekly, fortnightly, monthly)** | **Score**  | **Discontinuation criteria ANC (mm3/L)†** | **Score**  | **Discontinuation criteria WCC (mm3/L)†** | **Score**  | **Rechallenge restrictions** | **Score**  | **Modified BEN criteria** | **Score**  |
| None | 0 | None | 0 | None  | 0 | None | 0 | None | 0 | Yes | 0 |
| ANC  | 1 | 4, ✗, >4  | 1 | ANC <0.5 | 1 | WCC <1.0  | 1 | Off-licence agreement  | 1 | None  | 1 |
| WCC | 2 | 12, ✗, >13-52  | 2 | ANC <1.0  | 2 | WCC <2.0  | 2 | Index ANC count  | 2 |  |  |
| ANC & WCC  | 3 | 18, ✗, >19  | 3 | ANC <1.5  | 3 | WCC <3.0  | 3 | Index WCC & ANC count  | 3 |  |  |
|  |  | 18, 19-51, >52  | 4 |  |  | WCC <3.5 | 4 | Full  | 4 |  |  |
|  |  | 26, 27-51, >52  | 5 |  |  | WCC <4.0 | 5 |  |  |  |  |
|  |  | 24, 24, ✗  | 6 |  |  |  |  |  |  |  |  |
| **Abbreviations** ANC; Absolute neutrophil count BEN; Benign ethnic neutropenia WCC; white cell count **Notes**†Where countries used a graded approach, the most stringent threshold was used.  |

**Table 4. Unadjusted scoring**

|  |  |  |
| --- | --- | --- |
| **Indicator**  | **Weight (%)** | **Score adjustment if mandatory guidelines** |
| Monitoring parameter | 25 | Double score in table above  |
| Monitoring frequency | 25 | Double score in table above |
| Discontinuation criteria ANC | 15 | Double score in table above |
| Discontinuation criteria WCC | 15 | Double score in table above |
| Rechallenge restrictions | 10 |  |
| Modified BEN criteria | 10 |  |
| **Total**  | **100** |  |
| **Abbreviations** ANC; Absolute neutrophil count BEN; Benign ethnic neutropenia WCC; white cell count |

**Table 5. Weights of Indicators in the Composite Index**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Countries**  | **MP Score** | **MF Score** | **DC ANC Score** | **DC WCC Score** | **M BEN Score** | **RR Score** | **Stringency Index Score**  |
| ***Africa*** |  |  |  |  |  |  |  |
| Algeria  | 50 | 0 | 0 | 0 | 100 | 0 | 28 |
| Cameroon | 50 | 0 | 0 | 0 | 100 | 0 | 28 |
| Egypt  | 50 | 0 | 50 | 50 | 100 | 0 | 34 |
| Gabon | 50 | 33 | 50 | 50 | 100 | 0 | 12 |
| Ghana  | 0 | 0 | 0 | 0 | 100 | 0 | 28 |
| Guinea | 50 | 0 | 0 | 0 | 100 | 0 | 12 |
| Ivory Coast  | 0 | 0 | 0 | 0 | 100 | 0 | 28 |
| Kenya  | 50 | 0 | 0 | 0 | 100 | 0 | 12 |
| Libya | 0 | 0 | 0 | 0 | 100 | 0 | 12 |
| Malawi | 0 | 0 | 0 | 0 | 100 | 0 | 28 |
| Nigeria  | 50 | 0 | 0 | 0 | 100 | 0 | 28 |
| Ethiopia  | 50 | 0 | 0 | 0 | 100 | 0 | 45 |
| Somalia | 50 | 0 | 0 | 0 | 100 | 0 | 28 |
| South Africa | 17 | 0 | 33 | 0 | 0 | 0 | 6 |
| Sudan | 50 | 0 | 0 | 0 | 100 | 0 | 28 |
| Tanzania  | 0 | 0 | 0 | 0 | 100 | 0 | 12 |
| Tunisia  | 50 | 0 | 0 | 0 | 100 | 0 | 28 |
| Uganda  | 50 | 0 | 0 | 0 | 100 | 0 | 28 |
| Zambia | 50 | 0 | 50 | 50 | 100 | 0 | 34 |
| Zimbabwe  | 50 | 0 | 0 | 0 | 100 | 0 | 28 |
| ***Asia*** |  |  |  |  |  |  |  |
| Bangladesh | 50 | 42 | 0 | 83 | 100 | 0 | 28 |
| Bhutan | 50 | 0 | 0 | 0 | 100 | 0 | 28 |
| Cambodia | 50 | 0 | 0 | 0 | 100 | 0 | 12 |
| Hong Kong  | 0 | 0 | 0 | 0 | 100 | 0 | 72 |
| Israel  | 50 | 50 | 33 | 33 | 100 | 0 | 27 |
| Japan | 100 | 50 | 100 | 100 | 100 | 0 | 100 |
| India  | 50 | 0 | 0 | 0 | 100 | 0 | 28 |
| Iran | 50 | 0 | 50 | 67 | 100 | 0 | 36 |
| Malaysia | 33 | 50 | 67 | 0 | 0 | 0 | 84 |
| Jordan | 100 | 100 | 100 | 100 | 100 | 100 | 28 |
| Saudi Arabia  | 50 | 0 | 0 | 0 | 100 | 0 | 84 |
| Singapore  | 17 | 33 | 33 | 0 | 100 | 0 | 78 |
| Nepal  | 100 | 50 | 100 | 100 | 100 | 100 | 28 |
| North Korea | 50 | 0 | 0 | 0 | 100 | 0 | 23 |
| Armenia | 33 | 0 | 0 | 0 | 100 | 0 | 50 |
| Oman  | 50 | 0 | 0 | 0 | 100 | 0 | 28 |
| China  | 50 | 33 | 50 | 50 | 0 | 50 | 48 |
| Lebanon  | 100 | 50 | 100 | 100 | 100 | 100 | 29 |
| Qatar  | 100 | 50 | 100 | 100 | 100 | 50 | 39 |
| South Korea  | 50 | 25 | 50 | 50 | 100 | 100 | 55 |
| Sri Lanka | 50 | 33 | 0 | 0 | 100 | 0 | 38 |
| Thailand | 50 | 25 | 17 | 17 | 100 | 0 | 28 |
| Taiwan | 50 | 0 | 0 | 0 | 100 | 0 | 38 |
| Yemen | 50 | 0 | 0 | 0 | 100 | 0 | 28 |
| Albania  | 50 | 0 | 50 | 50 | 100 | 100 | 47 |
| ***Europe*** |  |  |  |  |  |  |  |
| Austria  | 100 | 50 | 100 | 100 | 100 | 100 | 84 |
| Belgium | 100 | 0 | 100 | 100 | 100 | 100 | 84 |
| Azerbaijan | 100 | 50 | 100 | 100 | 100 | 100 | 69 |
| Croatia  | 50 | 8 | 0 | 0 | 100 | 100 | 84 |
| Cyprus  | 100 | 50 | 100 | 100 | 100 | 100 | 59 |
| Czech Republic | 100 | 50 | 0 | 0 | 100 | 0 | 84 |
| Denmark | 100 | 50 | 100 | 100 | 100 | 100 | 84 |
| Estonia  | 100 | 50 | 100 | 100 | 100 | 100 | 84 |
| France  | 100 | 50 | 100 | 100 | 100 | 100 | 84 |
| Germany  | 50 | 25 | 50 | 50 | 100 | 100 | 84 |
| Greece  | 100 | 50 | 100 | 100 | 100 | 100 | 84 |
| Hungary  | 100 | 50 | 100 | 100 | 100 | 100 | 84 |
| Ireland | 100 | 50 | 100 | 100 | 100 | 100 | 90 |
| Italy | 100 | 50 | 100 | 100 | 100 | 100 | 84 |
| Latvia  | 50 | 25 | 50 | 50 | 0 | 100 | 84 |
| Lithuania | 100 | 67 | 100 | 100 | 100 | 100 | 84 |
| Luxembourg  | 100 | 50 | 100 | 100 | 100 | 100 | 84 |
| Malta  | 100 | 50 | 100 | 100 | 100 | 100 | 90 |
| Netherlands | 100 | 50 | 100 | 100 | 100 | 100 | 84 |
| Norway  | 100 | 50 | 100 | 100 | 100 | 100 | 84 |
| Romania | 100 | 67 | 100 | 100 | 100 | 100 | 84 |
| Russia  | 100 | 50 | 100 | 100 | 100 | 100 | 84 |
| Slovakia  | 100 | 50 | 100 | 100 | 100 | 100 | 84 |
| Slovenia | 50 | 25 | 50 | 50 | 100 | 100 | 84 |
| Sweden | 50 | 25 | 50 | 50 | 100 | 100 | 84 |
| Switzerland | 100 | 50 | 100 | 100 | 100 | 100 | 84 |
| Turkey | 100 | 50 | 100 | 100 | 100 | 100 | 81 |
| United Kingdom | 100 | 50 | 100 | 100 | 100 | 100 | 68 |
| Bulgaria | 100 | 50 | 100 | 100 | 100 | 100 | 43 |
| Finland | 50 | 25 | 50 | 50 | 100 | 100 | 55 |
| Iceland | 100 | 50 | 100 | 100 | 100 | 100 | 42 |
| Poland | 100 | 50 | 100 | 100 | 100 | 100 | 55 |
| Portugal  | 100 | 50 | 100 | 100 | 100 | 75 | 55 |
| Spain | 100 | 67 | 100 | 100 | 0 | 25 | 55 |
| ***North America*** |  |  |  |  |  |  |  |
| Costa Rica | 50 | 25 | 50 | 50 | 100 | 0 | 42 |
| Barbados  | 50 | 0 | 0 | 0 | 100 | 0 | 28 |
| Canada  | 100 | 83 | 100 | 67 | 0 | 25 | 69 |
| United States  | 50 | 25 | 50 | 0 | 100 | 100 | 37 |
| El Savador | 50 | 17 | 0 | 0 | 100 | 0 | 49 |
| Mexico | 50 | 0 | 0 | 0 | 100 | 0 | 33 |
| St Lucia | 33 | 83 | 67 | 0 | 0 | 0 | 28 |
| ***Australia and Oceania***  |  |  |  |  |  |  |  |
| Australia  | 100 | 50 | 100 | 100 | 100 | 25 | 75 |
| Fiji | 100 | 0 | 0 | 0 | 100 | 100 | 56 |
| New Zealand | 100 | 50 | 100 | 100 | 100 | 100 | 84 |
| Papua New Guinea | 0 | 0 | 0 | 0 | 100 | 0 | 12 |
| Tonga | 0 | 0 | 0 | 0 | 100 | 0 | 12 |
| ***South America*** |  |  |  |  |  |  |  |
| Argentina  | 100 | 50 | 100 | 100 | 100 | 75 | 81 |
| Brazil  | 50 | 0 | 0 | 0 | 100 | 0 | 78 |
| Bolivia  | 100 | 50 | 100 | 100 | 100 | 50 | 28 |
| Chile  | 33 | 50 | 67 | 0 | 100 | 0 | 40 |
| Guyana  | 33 | 17 | 0 | 67 | 100 | 0 | 12 |
| Paraguay  | 50 | 50 | 0 | 0 | 100 | 0 | 12 |
| Peru | 0 | 0 | 0 | 0 | 100 | 0 | 41 |
| Colombia  | 0 | 0 | 0 | 0 | 100 | 0 | 35 |
| Ecuador | 50 | 0 | 33 | 0 | 100 | 100 | 43 |
| Uruguay | 50 | 25 | 50 | 50 | 100 | 100 | 55 |
| Venezuela | 50 | 0 | 0 | 0 | 100 | 0 | 28 |
| Abbreviations ANC; Absolute neutrophil count BEN; Benign ethnic neutropenia DC ANC; Discontinuation criteria ANC DC WCC; Discontinuation criteria WCC M BEN; Modified BEN criteria MF; Monitoring frequency MP; Monitoring parameter RR; Rechallenge restrictions |

|  |  |  |  |
| --- | --- | --- | --- |
| **Continent**  | **Mean score (SD)** | **Range**  | **Median score (IQR)** |
| Africa  | 24.4 (9.6) | 39 (45 - 6) | 28 (12-28) |
|  Asia  | 43.2 (40.0) | 88 (100 – 12) | 32.5 (28 – 52.5) |
| Europe  | 75.9 (14.2) | 48 (90 – 42) | 84 (68 – 84)  |
| North America | 40.9 (13.5) | 41 (69 – 28) | 37 (28 – 49)  |
| Oceania and Australia  | 47.8 (30.6) | 72 (84 – 12)  | 56 (12 – 79.5) |
| South America | 41.2 (21.8) | 69 (81 – 12)  |  40 (28 -55) |
| **Abbreviations** IQR: Interquartile range SD; Standard Deviation |

**Table 6. Mean, Median and range of stringency index scores by continent**

**Supplementary Material 4:** Choropleth map of modified BEN monitoring guidelines. Red indicates no BEN monitoring criteria and yellow indicates presence of modified BEN monitoring criteria. Grey indicates no data.



Figure 1. BEN choropleth