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## LETTER

## Remarkable international variability in reasons for ineligibility and non-participation in the GLORIA trial

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Recruitment of patients in randomized controlled trials is a well-known problem. Recruitment may be difficult and often takes more time than expected. Most trials adapt their recruitment target or extend the inclusion period. A review of two reports from the UK noted that only 56% and 69% of the trials achieved their original recruitment target (1).

The international GLORIA (Glucocorticoid Low-dose Outcome in Rheumatoid Arthritis) trial also faces recruitment challenges. GLORIA is an ongoing large pragmatic trial that examines the harm, benefit, and costs of low-dose glucocorticoids (GCs) added to the standard treatment of rheumatoid arthritis (RA) patients aged 65 years or older. The eligibility criteria are non-restrictive: RA, age  $\geq 65$  years, 28-joint Disease Activity Score (DAS28)  $\geq 2.6$ , and no current GC treatment. Patients with comorbidity are expressly included, and the impact of trial procedures on normal care is minimal. Based on the screening logs of interested centres, we estimated that 4% of RA patients aged  $\geq 65$  would enter the study, and prepared accordingly. We have prospectively sampled all the reasons for ineligibility across a number of centres in different countries participating in the GLORIA trial.

Rheumatologists from eight centres in Germany, Hungary, The Netherlands, Portugal, and Romania screened the patient list of at least two full clinic days. For each patient, the eligibility and all possible reasons for exclusion were recorded by the treating rheumatologist.

In total, 385 RA patients were screened in January 2018. Of these patients, 15 (4%) were eligible to participate in the GLORIA trial. In Germany, Romania, and Portugal (Lisbon), all of the screened patients were ineligible.

About half of the patients (51%) had more than one reason for ineligibility. The most common reasons for ineligibility were inactive disease and age (both 58%

(Table 1). Current GC use was reported in 28%, 5% had a temporary reason (i.e. recent switch of therapy or GC use), and 11% had another reason for ineligibility. Other reasons were comorbidity, unwillingness of the patient to participate, participation in another trial, language barriers, or contraindication to prednisolone. We found remarkable differences between the sites in the proportion of patients with low disease activity versus those currently on GC therapy (Table 1).

Of the eligible patients, one was already participating, four were included after this screening, and one was currently considering participation; nine declined participation (most common reasons: fear of GCs, not interested in participating, preference for GC injections, or declining additional therapy). In all, about 1% of screened patients were included in the trial.

In our prospective study, we found remarkable differences between countries in reasons for non-participation in the GLORIA trial. GC use was very high in Lisbon (Portugal) and Berlin (Germany), while it was very low in another city in Portugal (Coimbra) and in The Netherlands. There could be several reasons for these differences, such as cultural differences or perhaps more severe RA in Lisbon and Berlin. In addition, GC use may already be common practice among some of the rheumatologists. The information needed to clarify these differences is not available.

The willingness of eligible patients to participate in the GLORIA trial was low in this elderly population, despite the pragmatic design and low effort required to participate. Earlier studies also showed that it is challenging to include elderly patients in clinical trials (2, 3). Our experience resembles that of another large international clinical trial: the inclusion duration was extended, 3984 patients were screened, 8% were eligible, but 2% refused participation

Table 1. Patients ineligible for the GLORIA trial, by country and reason.\*

| Centre          | n   | Percentage ineligible because of: |                  |            |                     |       |
|-----------------|-----|-----------------------------------|------------------|------------|---------------------|-------|
|                 |     | Age                               | Disease activity | Current GC | Temporary exclusion | Other |
| Total           | 370 | 58                                | 58               | 28         | 5                   | 11    |
| The Netherlands |     |                                   |                  |            |                     |       |
| Amsterdam       | 158 | 54                                | 70               | 22         | 5                   | 11    |
| Rotterdam       | 43  | 63                                | 58               | 12         | 2                   | 9     |
| Leeuwarden      | 47  | 51                                | 70               | 11         | 4                   | 19    |
| Germany         |     |                                   |                  |            |                     |       |
| Berlin          | 23  | 52                                | 52               | 65         | 0                   | 17    |
| Portugal        |     |                                   |                  |            |                     |       |
| Coimbra         | 24  | 58                                | 21               | 8          | 4                   | 17    |
| Lisbon          | 10  | 60                                | 60               | 80         | 80                  | 10    |
| Hungary         |     |                                   |                  |            |                     |       |
| Debrecen        | 47  | 75                                | 43               | 55         | 0                   | 2     |
| Romania         |     |                                   |                  |            |                     |       |
| Bucharest       | 18  | 56                                | 22               | 44         | 0                   | 6     |

\*Patients can have more than one reason.

GLORIA, Glucocorticoid Low-dose Outcome in Rheumatoid Arthritis; GC, glucocorticoid.

(4). Finally, a literature review found comparable reasons for the limited recruitment of patients in trials, i.e. unwillingness to be randomized, preference for a specific treatment, and a lack of eligible patients (5).

In conclusion, recruitment takes more time than planned in the majority of trials (1, 4) because eligibility is low and patients frequently decline participation (4, 5). Prescreening of patients at potential sites can provide important information on the potential to recruit patients in a trial, but the actual willingness of patients to participate remains hard to predict.

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