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. The recruitment of patients may be difficult and often takes more time than expected. Most trials adapt their recruitment target or extend the inclusion period. Two recent reports from the United Kingdom noted that only 56 resp. 69% of the trials achieved their original recruitment target (1).

The international GLORIA trial also faces recruitment challenges. GLORIA is an ongoing large pragmatic trial that examines harm, benefit and costs of low-dose glucocorticoids (GCs) added to the standard treatment of rheumatoid arthritis (RA) patients of 65 years or older. The eligibility criteria are non-restrictive: RA, age ≥65 years, disease activity score (DAS28) ≥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 screening logs of interested centres, we estimated 4% of RA patients aged ≥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 8 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 of 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 patient to participate, participation in another trial, language barrier or contra-indication to prednisolone. We found remarkable differences between the sites in the proportion of patients with low disease activity vs. those currently on GC therapy (Table 1).

Of the eligible patients, 1 was already participating, 4 were included after this screening, and 1 was currently considering participation; 9 declined participation (most common reasons: fear of GCs, not interested to participate, 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 in another city in Portugal (Coimbra) and in The Netherlands the GC use was very low. There could be several reasons to clarify these differences, such as cultural differences or maybe more severe RA in Lisbon and Berlin. In addition, GC use might be already common practice among some of the rheumatologists. The information 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 to participate. Earlier studies also showed that it is challenging to include elderly patients in a clinical trial (2, 3). Our experience resembles that of another large international clinical trial: inclusion duration was extended, 3984 patients were screened, 8% were eligible, but 2% refused participation (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 the trials (1, 4) because eligibility is low and patients frequently decline participation (4, 5). Pre-screening 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.

Key words
Randomized controlled trial, recruitment, ineligibility

Table 1: Patients ineligible for the GLORIA trial, by country and reason (patients can have more than one reason).

		Percent ineligible for:				
Centre	**n**	**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

Ethics approval and consent to participate
Not applicable.

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Conflict of interest
None.

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