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Challenges and opportunities for oral-systemic interventional studies

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1 **Challenges and opportunities for oral-systemic interventional studies**

2
3 We welcome the recent JDR paper discussing the methodological issues surrounding
4 research into the relationships between oral and systemic diseases (Raittio and Farmer
5 2021).

6
7 We offer some additional thoughts, that are specific for clinical studies, where periodontitis
8 is the exposure and its management is the intervention whilst the progression and/or
9 severity of the systemic disease (or associated complications) are the outcome measures.
10 Key limitations include: short follow-up time of study participants, the use of surrogate
11 systemic endpoints, inconsistent inclusion criteria, a failure to control the exposure to target
12 endpoints of success, and small sample sizes. The first two result from the ethical concerns
13 around withholding or delaying the treatment of periodontitis for control arm participants.
14 Furthermore, several trials were single-centre studies thus reducing the generalizability of
15 the findings. However, as McNamara's Fallacy suggests, just because something is difficult
16 to measure, it doesn't mean that it doesn't exist.(Kelleher 2021) Compelling evidence of
17 association is emerging across several systemic diseases. (Hirschfeld and Chapple 2021)

18
19 These significant methodological challenges demonstrate the need to explore innovative
20 solutions (Watt and Serban 2020). The UK established PROSpECT (Periodontal Research on
21 Multimorbidity and Systemic Health Clinical Study Group and Research Consortium)
22 encourages collaborative working to create methodological consensus for parameters of
23 study design. PROSpECT has achieved consensus for several study design gaps – establishing
24 intervention and control arm criteria, target endpoints, standardised criteria for treatment
25 success, recruitment strategies, and follow-up duration, important steps in designing robust
26 studies.(Pavitt 2020)

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31 All authors listed have made a substantial, direct and intellectual contribution to the work.

32 All authors gave their final approval and agree to be accountable for all aspects of the work.

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