Enrollment of Neonates in More Than One Clinical Trial

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ABSTRACT

Because the highest rates of morbidity and mortality in neonates are seen in those born at <32 weeks' gestation, this group has the most urgent need for novel therapies to improve survival and outcome. Legislative efforts in the United States and Europe have attempted to address this issue by requiring the study of drugs, biological and nutritional products, devices, and other therapies in this population through a combination of high-quality regulatory and clinical trials, quality improvement initiatives, and observational studies. Because there are relatively small numbers of very preterm neonates born each year in any 1 country or continent, and because a significant number of clinical trials are recruiting at any 1 time, a neonate may meet enrollment criteria for >1 clinical trial. Neonatal units that have the infrastructure and resources to engage in research frequently face the question of whether it is permissible to enroll a neonate in >1 trial. This article examines the pertinent scientific, ethical, regulatory, and industry issues that should be taken into account when considering enrolling neonates in multiple clinical studies. (*Clin Ther.* 2017;39:1959–1969) © 2017 The Authors. Published by Elsevier HS Journals, Inc.

Key words: neonate, clinical trial, co-enrollment.

INTRODUCTION

Many common neonatal care practices and therapies have never been rigorously evaluated with adequate efficacy and safety data to support formal regulatory approval. As a result, most treatments have evolved into "best practice" and "standard of care" with insufficient evidence to support safety, efficacy, dosage, and treatment exposure. The compelling need to advance neonatal drug development has been recognized and has resulted in US and European legislation mandating more studies in this unique population. To develop the tools, standards, and approaches needed to accomplish this goal, the US Food and Drug Administration (FDA) and the Critical Path Institute, with support from the pharmaceutical industry, established the International Neonatal Consortium. This consortium brings together regulators, neonatologists, nurses, pharmaceutical companies, funding organizations, and parent/community groups to advance

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regulatory science and address the needs of neonates.[1,2] However, neonates are seen as a highly vulnerable population, with their participation in drug development and clinical trials limited by numerous factors.

Because the highest rates of morbidity and mortality are seen in neonates born at <32 weeks' gestation, this group has the most urgent need for novel therapies to improve survival and outcome. Because a small fraction of live births occur at <32 weeks' gestation (1.5% in the United States),[3] there are numerous clinical trials recruiting at any 1 time and a relatively small population of premature or ill neonates available for enrollment. A country-wide sampling of the annual number of preterm neonates born before 32 weeks' gestation revealed ~3500 in Canada in 2012,[4] 8300 in England and Wales in 2015,[5] 7100 in Japan in 2015,[6] and 63,000 in the United States in 2015.[3] The expertise and resources needed to conduct these studies tend to be concentrated in a limited number of neonatal intensive care units, where most neonates may be eligible to participate in >1 clinical trial at a time.[7] To continue to successfully improve neonatal survival and outcome, we must study drugs, biological and nutritional products, devices, and other therapies in parallel through a combination of high-quality clinical trials, quality improvement initiatives, and noninterventional studies. With the constraints of the small population of eligible neonates, progress will be limited unless alternatives to restricting enrollment to a single clinical trial are considered, including developing new methods and study designs. The present article examines the pertinent issues that should be considered when enrolling neonates in multiple studies.

SCIENTIFIC CONSIDERATIONS WHEN ENROLLING A NEONATE IN >1 CLINICAL TRIAL

An initial approach is to consider the goal of clinical research, which is to gather reliable information about the balance between safety and efficacy for each product or intervention under investigation. Although each trial seeks to standardize research-related variables, there is the additional challenge of practice variability that occurs within and among neonatal intensive care units. Although this "background noise" may preclude detection of an effect of the intervention being tested, allowing practice variations may better simulate how the intervention performs under real-world conditions. When deciding whether to allow enrollment of neonates in >1 study, the impact of practice variability on interpretation of study results should be considered.

How will enrollment of neonates in >1 trial affect the validity of each individual trial? Each trial describes clinical events with some level of accuracy, attributes clinical events to 1 or more products or interventions, and assigns a degree of reliability to the description and attributions. These characteristics lead to hazards that may arise in all trials, which can include the following: (1) detection errors—the trial may fail to describe an event because the event is too rare, the event is not detected due to investigator error, or there is a failure in data collection; (2) misattribution—the trial may falsely attribute an event to the intervention or may fail to attribute an event to the trial; and (3) uncertainty—the information may not be precise enough for its intended use.

The extent to which these hazards may occur is variable and can lead to consequences of misattribution or uncertainty, such as: (1) reducing the precision of estimates of safety or efficacy, including altered effect size if the interventions have opposite effects or if the interventions are synergistic; (2) misattributing events that could contribute to assessments of safety or efficacy to 1 intervention or another (trial or nontrial related); and (3) alterations in drug disposition related to enzyme induction or drug effects (eg, competitive antagonism at a receptor that is the intended or an unintended target) that will depend on the temporal relationship between administration of the interventions. During early-phase trials, proximate consequences could include imprecision in pharmacokinetic (PK) or PK/pharmacodynamic (PD) relationships.

Drug–drug interactions are a major concern for concurrent studies. Pharmacologic (eg, medications for pain) or nonpharmacologic (eg, kangaroo care for pain) interventions may ameliorate or exaggerate the true effect of each intervention. The following types of interactions are determinants of the intensity, quality, or duration of drug response: (1) PK interactions in which 1 drug inhibits or accelerates metabolism and elimination of the other; (2) PD interactions in which drugs may act at the receptor or effector level, masking the true effect of the interventions; or (3) simple chemical incompatibilities, which would negate the

effects of the drugs being given together. The need to perform requisite evaluations of drugs for neonates must address this conundrum with respect to drug interactions.

Early-phase clinical trials require definition of true pharmacologic effects on safety and potential efficacy in a small number of neonates. Simultaneous co-enrollment should be avoided to generate accurate PK data and evaluate PD variables with minimal interactions, to allow proper design of advanced protocols. In randomized trials, studying ≥2 drugs or nonpharmacologic interventions with known interactions of any type should be avoided. Convenience sampling from neonates who receive multiple medications for clinical indications with known interactions (eg, drugs for patent ductus arteriosus closure and aminoglycosides) may be useful.

STRATEGIES TO CONSIDER WHEN PLANNING FOR CO-ENROLLMENT

Although enrollment in >1 clinical trial can be highly problematic, there are other instances in which it may be permissible (Table I). For example, enrollment in >1 simultaneous or sequential clinical trial should be avoided if the primary end points of the 2 trials are similar, as attribution of main effects to 1 or the other trial would be extremely difficult. The exception would be if the trials were combined in a factorial design, in which participants are randomized to 1 or more interventions from the outset (ie, 4 arms including standard of care, intervention A, intervention B, and interventions A + B). The impact of each arm's treatment on the primary end point can then be evaluated. However, factorial trials require a substantial increase in the sample size to evaluate interactions between interventions.[8–10]

Enrollment in >1 trial should also generally be avoided when each of the trials is evaluating a novel therapy because the disposition of the new drugs may not be well characterized, and robust safety or efficacy information may not be available. Drugs that are not approved or marketed for a neonatal indication, but have been widely studied and are considered current standards of care, may not be subject to this restriction if other criteria are met for safety evaluation and scientific integrity.

There are several scenarios in which enrollment in >1 trial is unlikely to compromise safety or scientific validity of either trial. Short PK and/or safety studies or device validation studies separated by a scientifically determined period of time from an interventional study may be permissible. In the review by Myles et al[9] of ethical and scientific considerations for concurrent enrollment, co-enrollment may be permitted if the following 3 conditions are met: (1) the likelihood of enrollment in study B has not been influenced by treatment in study A; (2) if neither treatment influences the natural course of disease of the other condition being studied; and (3) if there is unlikely to be a drug–drug interaction. The review highlights consideration of the potential increased burden of various study procedures as well as sample size adjustments and potential selection biases.

If co-enrollment is considered, it will require exploration of scientific details, including: (1) the temporal relationship between the antecedents of the effects (whether the causal pathways of the relevant events overlap in time); (2) what is known about the treatment (s); (3) the phase of development for each product; (4) the temporal relationships between interventions in each trial; (5) whether there are overlapping absorption, distribution, metabolism, and excretion pathways; (6) whether there are potentially overlapping toxicities; and

Table I. Co-enrollment in clinical trials.

Avoid Co-enrollment	Co-enrollment May be Permissible
Early-phase PK studies	Brief pharmacokinetic and or safety/studies
Randomized trials studying ≥2 drugs or interventions with known interactions	Device validation studies
Trials with similar primary end points	Factorial study designs with adequate sample sizes
If each trial is specifically targeting the same organ system	Trials of drugs routinely used and considered standard of care for neonates

(7) whether enrollment in an additional study may be treated as a covariate in the statistical analysis.

Comparative effectiveness trials, in which ≥2 accepted strategies or treatments are being evaluated, may use the covariate strategy to enable co-enrollment. Because the potential for co-enrollment is high in neonatal studies, it should be considered during protocol development. Absolute decisions about co-enrollment should be avoided, and specific language addressing when co-enrollment may or may not be permissible should be included in protocols. Specific limitations should be based on informed, well-reasoned judgment or statistical criteria. Other strategies that may be considered when planning neonatal studies in which the question of co-enrollment could arise include: (1) accepting a low level of co-enrollment when it is believed to be unlikely to lead to serious consequences and may facilitate recruitment; (2) adopting a conservative approach with no co-enrollment allowed, which may lead to difficulty finding an adequate number of study sites, increased competition among studies, and ultimately slow research progress; and (3) clinical trial simulation and modeling to generate quantitative estimates of the range and magnitude of the risks and/or interactions.

In summary, the scientific validity of a clinical trial may be undermined by co-enrollment through a potential effect on the statistical power of the individual trials and/or an interaction between the 2 interventions.[7,9] An interaction may also lead to different conclusions about safety and/or efficacy of 1 or both interventions that might not have been apparent in separate clinical trials.[9,10] In addition to concerns about statistical power, increased risk of adverse events (AEs), and the interpretation of study results, there may be a problem with outcome ascertainment bias.[11] Thus, whether to allow co-enrollment in >1 clinical trial requires a careful assessment of the potential impact on the study results, interactions between the interventions, subject safety, and the scientific validity of the clinical trials.[12–15]

ETHICAL CONSIDERATIONS WHEN ENROLLING A NEONATE IN >1 CLINICAL TRIAL

The primary principle to consider as stated by the International Conference on Harmonisation in its Guideline for Good Clinical Practice (ICH-E6) is that the child's interest should always prevail over that of science and society. This principle is paramount when assessing and monitoring risks. There are several ethical issues that must be addressed if co-enrollment in >1 clinical trial is to be allowed: (1) co-enrollment may inadvertently increase the risks and burdens beyond those that would otherwise have been allowable for each clinical trial considered alone, especially for nonbeneficial (eg, "research only") procedures such as blood draws; (2) the impact of either allowing or disallowing co-enrollment in >1 clinical trial on parental decision-making must be considered; and (3) co-enrollment must not undermine the scientific validity of either clinical trial.

Parental Permission

Not allowing parents to co-enroll their neonates in studies that they would want to support and whose risks and benefits have been explained to them seems to restrict their right to exercise such choices on behalf of their neonate.[9] Although it may be reasonable to restrict co-enrollment if it would undermine the scientific validity of the clinical trials, this approach does not address the question of which clinical trial should be offered to the parent(s). Allowing co-enrollment, when scientifically appropriate, respects the role of parents in deciding for their neonate and may result in a more representative population of those neonates who would receive the 2 interventions in clinical practice.[7,9,11] There are no data to indicate that it may be too stressful and thus unethical to approach parents about co-enrollment in multiple studies.[10] One study showed that most mothers of neonates were willing to participate in >1 study.[7] In another study, most parents (74%) of preterm neonates were comfortable with enrollment in >1 study at any one time with a minority (22%) being worried about the number of studies.[16] Co-enrollment did not seem to have an impact on recruitment.[13]

When co-enrollment is an appropriate option (whether at the same time or in sequence), parents should be fully informed about the available studies, including any potential interactions between the studies (eg, the chances of an unknown drug–drug interaction). Although it seems that parents are generally supportive of co-enrollment, it is important to recognize that having a critically ill neonate can be difficult, and parents should be supported throughout the entire clinical trials process.[16–18]

Risks and Burdens of Participation

According to FDA regulations, a nonbeneficial (or "research only") procedure must present no more than minimal risk (21 CFR 50.51) or no more than a minor increase over minimal risk (21 CFR 50.53). Outside of the United States, existing regulations and/or guidance limit such procedures to no more than minimal risk, yet neither define minimal risk nor define it as comparable to the routine clinical experience of the enrolled research population.[19] This approach is the one taken by the addendum to the ICH E-11 to harmonize the United States with other approaches. Within the United States, minimal risk is usually limited to routine physical and psychological examinations of healthy children. The category of minor increase over minimal risk is not defined but is limited to children with the disorder or condition (suggesting that this level of risk is similar to the routine clinical care of children enrolled in the research, consistent with international guidance on minimal risk). Perhaps for this reason, ICH E-6 uses the term "low risk" to describe the appropriate risk level for nonbeneficial procedures performed on individuals who are unable to consent for themselves. An individual procedure may qualify as either minimal risk or a minor increase over minimal risk, but when performed multiple times over a limited period of time, the overall risk may exceed an acceptable threshold. Thus, co-enrollment may result in a risk exposure that exceeds minimal risk/minor increase over minimal risk. As such, a research ethics committee should be aware of the possibility of co-enrollment and approve this possibility in advance.

Observational studies may not involve a change in clinical treatment, but additional blood draws and/or monitoring could place an additional burden on a neonate. Although that burden for an individual study may be reasonable, the additive effects of multiple studies may be unreasonable.[7] Blood sampling for both clinical care and research must be coordinated to minimize discomfort and to keep the total volume of blood drawn within acceptable limits.[15]

REGULATORY CONSIDERATIONS WHEN ENROLLING A NEONATE IN >1 CLINICAL TRIAL

Regulatory agencies and the ICH have not issued comprehensive guidance regarding co-enrollment. Adherence to the principles of sound trial design and scientific validity is critical in the assessment of whether co-enrollment may be considered. Regulatory agencies, with their charge to protect the public health, must thoroughly consider the potential safety implications of any study design alongside its potential to demonstrate efficacy.

Although Health Canada does not have any regulations specific to pediatrics in general or neonates in particular, the conduct of clinical trials in children from birth to 18 years of age can be requested as necessary. Health Canada does have guidelines that allow for flexibility in regulatory decision-making, as long as a suitable scientific and clinical rationale is provided. This flexibility could potentially allow enrollment of neonates in >1 trial when deemed scientifically and ethically sound. Consideration should be given to the duration and timing of each study together with its measured outcomes, as well as the potential to use nonstandard or adaptive designs and analyses.

A pediatric investigation plan and/or waiver covering the entire pediatric population, including neonates, is mandatory for the authorization of a new medicinal product in the European Union. These are reviewed and agreed by the Paediatric Committee at the European Medicines Agency (EMA) in the framework of the Paediatric Regulation (Regulation [EC] No. 1901/2006). In addition, EMA can provide advice on clinical trial protocols through its Scientific Advice Working Party. Whereas co-enrollment is not specifically referred to and the considerations outlined in this article with respect to scientific, safety, and ethical considerations are valid, there are opportunities to discuss such approaches at EMA through scientific advice[20] or during the pediatric investigation plan procedure.[21] The authorization of clinical trials occurs at each member state level.[22]

Enrollment of neonates in >1 regulated clinical trial or 1 regulated trial and a non-FDA regulated trial has been permitted by the FDA in specific circumstances. The FDA Draft Guidance ("Informed Consent Information Sheet: Guidance for IRBs, Clinical Investigators, and Sponsors") issued in 2014 references participation in >1 clinical trial. The Draft Guidance states,[23] "FDA strongly discourages these practices as enrollment in >1 clinical investigation could increase risks to subjects, particularly because they may be exposed to >1 investigational product for which the safety profile may not be well

understood. Undoubtedly, enrollment of a single patient in studies of two or more novel agents would increase risk and potentially confound safety and efficacy assessments."

Many neonatal therapies have been used off-label for decades or longer. For those drugs, the safety profile may be reasonably well known. Clinical trials using standard therapies may be acceptable alongside a novel treatment trial as long as principles of scientific validity are met (separate target organ systems and/or primary end points). Regulatory agencies are also invested in the principles of parental permission and consent, and co-enrollment may be accompanied by specific considerations in the permission process. Although regulatory agencies may differ in approach to co-enrollment for neonatal trials, the fundamental concerns are consistent: retaining the scientific and statistical validity of individual studies, maintaining the ability to detect significant AEs, ensuring parental permission is both informed and voluntary, and, importantly, allowing access to investigational agents when there are no approved treatments for a given condition.

INDUSTRY CONSIDERATIONS WHEN ENROLLING NEONATES IN >1 CLINICAL TRIAL

Drug developers within pharmaceutical companies are keenly aware of the challenges of recruiting and performing neonatal clinical trials, especially with extremely preterm neonates. Enrollment can be exceedingly slow, even when performing trials to prevent bronchopulmonary dysplasia (BPD), 1 of the most common diseases affecting preterm neonates. An analysis of recruitment rates in large studies evaluating BPD prevention (as either a primary or secondary end point) was recently performed by Chiesi Farmaceutici. A total of 11 completed studies were identified, and the average enrollment duration was nearly 4 years, with 1 trial lasting >7 years. The average recruitment rate was 1.3 neonates/site/month, with a range of 0.4 to 4 (Table II).

These prolonged periods of enrollment have resulted in few drugs being adequately tested in neonates. Therefore, industry investigators support the concept of allowing participation in >1 study at a time for neonates who: (1) are cared for at sites with appropriate expertise; (2) have parents willing to have their neonate participate in research; and (3) meet entry criteria. However, co-enrollment must be carefully evaluated with the support of scientific review and regulatory guidance, to determine under which conditions this co-enrollment would be permissible.

First, one must assess the type of studies to be considered for co-enrollment. For example, studies of a preventative therapy for BPD at the same time as a preventative therapy for retinopathy of prematurity would be difficult to analyze, as these morbidities are believed to have common etiologies. However, a neonate who participated in an early prevention trial may later be considered for eligibility in a treatment trial for established complications of extreme prematurity.

Although many observational trials could be performed within the same timeframe as the investigational drug trial, the drug may have an impact on the results of the observational study. Nonpharmacologic studies (eg, nutritional agents) may be viewed to have small effects on drug study outcomes. However, poor growth during the neonatal period can affect neonatal morbidities as well as later neurodevelopmental outcomes. Thus, the challenge of studying a new investigational drug and discerning which AE or serious AEs can be ascribed to the new drug is challenging. Comprehensive safety and AE data are not available for the majority of neonatal therapies, and evaluating AEs with >1 investigational drug can therefore be difficult. If the event is serious, the uncertainty of the potential causative agent could place a promising compound at risk, not only for neonatal use but for even for older age groups.

Due to these concerns, many pharmaceutical companies have adopted a policy in which neonates may not be enrolled in a new trial until at least 30 days after the end of active participation in a previous trial. Operationally, there are also complications if the 2 studies are performed using agents developed by separate companies for which different standard operating procedures may exist and proprietary concerns pose challenges to data sharing. Trial procedures such as monitoring policies, consent processes, case report forms, data entry, and AE reporting may further complicate the studies and make them more prone to errors. Under the right scientific and operational circumstances, concomitant studies should be considered but only with very careful consideration of the proposed concomitant trials.

Table II. Neonatal trials evaluating BPD prevention (primary or secondary outcome): sites, recruitment and target population.

Trial Title	Actual Accrual (Patients)	No. of Sites (Centers)	Trial Start Date	Enrollment Period Close Date	Enrollment Duration (mo)	Recruitment Rate (Patients/ Site/Month)	Indication	Study Population
NIV Strategies for RDS in preterm infants. NIV (Noninvasive Ventilation), RDS (Respiratory Distress Syndrome) **(NIV)**	280	2	1/1/2010	12/1/2012	35	4	RDS of prematurity	VLBW infants (birth weight <1500 g and GA <32 wk)
Can omega 3 fatty acids improve respiratory outcomes in preterm infants. N3RO: (N-3 fatty acids for improvement of Respiratory Outcomes) **(N3RO)**	1273	13	6/18/2012	9/30/2015	39.39	2.49	Infant RDS (BPD prevention)	Preterm infants with RDS. <28 wk GA; 28–30 wk GA
Surfactant Positive Airway Pressure and Pulse Oximetry Trial in extremely low birth weight infants **(SUPPORT)**	1316	22	2/1/2005	5/3/2008	39	1.53	Premature birth; BPD prevention; retinopathy of prematurity	Extremely preterm infants (GA, 24 wk 0 d–27 wk 6 d)
Prematurity and Respiratory Outcomes Program **(PROP)**	835	13 (6 centers)	8/1/2011	4/1/2015	43	1.49	Prematurity; respiratory disease	Infants admitted to the NICU who are <29 wk GA
Efficacy and Safety of targeting lower arterial oxygen saturations to reduce oxygen toxicity	1201	25	12/24/2006	8/25/2010	44	1.09	Respiratory insufficiency of prematurity	Infants with GA of 23 wk 0 d through 27 wk 6 d

(continued)

Table II. (continued).

Trial Title	Actual Accrual (Patients)	No. of Sites (Centers)	Trial Start Date	Enrollment Period Close Date	Enrollment Duration (mo)	Recruitment Rate (Patients/ Site/Month)	Indication	Study Population
and oxidative stress in very preterm infants: The Canadian Oxygen Trial (COT)								
A randomized trial of standard versus higher oxygen saturation levels on long term growth and development in infants (BOOST)	358	8	9/15/1996	9/15/2000	48	0.93	Preterm infants	Infants born at <30 wk of gestation who remained dependent on supplemental oxygen at 32 wk of postmenstrual age
Efficacy and safety of methylxanthines in very low birthweight infants (CAP)	2000	34	10/1/1999	3/1/2007	89	0.66	Apnea of prematurity	Birth weight 500–1250 g
Efficacy and safety of inhaled budesonide in very preterm infants at risk for bronchopulmonary dysplasia (NEuroSIS)	863	40	4/1/2010	12/31/2012	33.02	0.65	BPD prevention	<28 wk GA
Trial of Late Surfactant for Prevention of Bronchopulmonary Dysplasia: A study in ventilated preterm	511	25	1/1/2010	1/1/2013	36	0.56	BPD prevention	<28 wk age

(continued)

Table II. (continued).

Trial Title	Actual Accrual (Patients)	No. of Sites (Centers)	Trial Start Date	Enrollment Period Close Date	Enrollment Duration (mo)	Recruitment Rate (Patients/ Site/Month)	Indication	Study Population
infants receiving inhaled nitric oxide (Surfactant Study) (TOLSURF)								
Inhaled Nitric Oxide (INO) for the Prevention of Bronchopulmonary Dysplasia (BPD) in Preterm Infants Requiring Mechanical Ventilation or Positive Pressure Support on Days 5–15 After Birth (NewNO)	451	33	11/1/2009	2/27/2012	27.9	0.49	Infant RDS (BPD prevention)	Preterm infants with RDS. <28 wk GA, 28–30 wk GA
Early Prevention of bronchopulmonary Dysplasia and Neonatal Mortality in Very Preterm Infants Using Low Dose of Hydrocortisone: A Randomized Controlled Trial (PREMILOC)	523	21	5/25/2008	1/31/2014	68	0.36	BPD prevention	<28 wk GA

Source: Chiesi Farmaceutici (Scientific Information Dept. - G. Mazzola).
BPD = bronchopulmonary dysplasia; GA = gestational age; NICU = neonatal intensive care unit; RDS = respiratory distress syndrome; VLBW = very-low-birth-weight.

CONCLUSIONS

Provided that the scientific, ethical, and safety aspects of co-enrollment can be adequately addressed, there should be no barrier to the co-enrollment of eligible neonates in >1 clinical trial. Careful consideration of the risks and benefits both to the neonate and to the research studies must occur before any co-enrollment. Although participation in >1 clinical trial using similar therapeutic targets and/or primary outcome measures should be discouraged, studies involving various conditions that involve a different therapeutic target organ and different primary outcome measures may be permitted following agreements between the investigators, sponsors, and other regulatory bodies. The regulatory agencies consider adequate safety monitoring, scientific rigor and validity, and informed, voluntary parental consent to be paramount. In addition to facilitating more rapid enrollment in much-needed neonatal clinical trials, co-enrollment may allow for access to investigational agents for conditions without approved therapies.

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CONFLICTS OF INTEREST

Linda Storari works for Chiesi Farmaceutici SpA, Ronald Portman works for Novartis, and Simin Baygani works for Eli Lilly. Otherwise no other COI.

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