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Recruitment Considerations for Early Phase Clinical Trials in Diabetes

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Key Focus Points

- Patient participation in early phase clinical trials in diabetes can reduce risks and accelerate “go, no-go” decisions
- Early phase clinical trials that recruit patients with diabetes require appropriate inclusion/exclusion criteria that consider comorbidities and concomitant medications thereby protecting the safety of participants while providing useful information
- Older patients, those in the pediatric and adolescent age groups, and women of childbearing potential require specific risk management strategies

Introduction

Scientists engaged in translational clinical research strive to transform laboratory discoveries into safe and effective new therapies. A critical step in translational science is the move from preclinical animal studies to human testing. Information from well-designed early phase clinical trials can potentially shorten the early clinical development of therapeutic compounds and reduce the time to access of new treatments. In this article we consider the use of patients in early phase studies with particular reference to the evaluation of new drugs for diabetes.

Selection of the Study Population

A key design consideration for early phase clinical trials involves selection of the study population. There are merits in using subjects drawn from the target population for the investigational agent. The choice of subject population depends on ethical considerations and the scientific and research objectives of the study. Recruitment decisions must be sensitive to the need for protection of participants and sharing of the burden of participation across the entire population, while fulfilling a 'best data' criterion that balances potential risks and benefits.

In the context of new drugs for diabetes, either healthy volunteers or patients with stable diabetes may be recruited. Healthy volunteers are often used to test investigational agents. This approach can provide good quality data since the effects of a study intervention can be separated from those caused by disease, comorbidities, or concomitant medications. Healthy volunteers may tolerate adverse effects from investigational agents better than patients; however, they can sometimes experience harm.

Patients with stable disease may also serve as subjects, although this approach is not accepted in all regulatory environments. Patients with stable disease can provide the most informative data, as the target of the investigational agent exists only in people with the particular health problem. Patients with stable disease are sometimes considered most suitable if early phase clinical studies are too risky for healthy people; however, they also face high relative risks with little or no potential benefit. These considerations rarely apply to diabetes but are of relevance other therapeutic areas such as oncology.

Early Phase Clinical Trials in Type 2 Diabetes

Patients with type 2 diabetes often participate in early phase clinical trials, including first-in-human trials. Certain risks may be reduced, e.g. insulin resistant patients may be less likely to experience hypoglycemia in response to a glucose-lowering agent compared to non-diabetic subjects. "Go, no-go" decisions may be accelerated, as a non-efficacy signal may be more easily confirmed in patients, potentially reducing unnecessary exposure of other subjects to investigational agents. Patients may benefit as individuals through participation in clinical trials. For example, screening may identify previously undiagnosed comorbidities, and patient education about diabetes, self-monitoring, and standards of care may be improved.

However, the participation of patients with type 2 diabetes in early phase clinical trials comes with challenges. Study subjects require careful risk management; there must be a willingness to accommodate comorbidities and concomitant medications that might be required. To address these challenges, appropriate inclusion and exclusion criteria must be provided in the clinical trial protocol to ensure that participants are not unnecessarily exposed to risk and that the study provides robust data.

Disease Status

An essential first criterion when selecting patient participants in the context of early phase clinical trials in diabetes is an assessment of disease status. An accurate diagnosis and classification should be made. For a study focused on type 2 diabetes the exclusion of type 1 diabetes or latent autoimmune diabetes is a prerequisite. Every patient should have an assessment of their recent glycaemic control. Hemoglobin A_{1c} (HbA_{1c}) levels must be within defined upper (e.g. 10-11%; 86-97 mmol/mol) and lower (e.g. 6.5% or 7%; 48-53 mmol/mol) boundaries to decrease risk for unacceptable hyperglycemia or hypoglycemia and provide uniformity of effects on outcomes measures and efficacy assessments (Figure 1). A medical evaluation of a patient's history regarding hypoglycemia will identify recurrent episodes of severe hypoglycemia, which puts patients at risk for future hypoglycemia and hypoglycemic unawareness. During clinical trials subjects must be capable of promptly alerting staff to symptoms of hypoglycemia since investigators and study staff are usually blinded to treatment randomization. Individuals who have lost their early warning symptoms of hypoglycaemia, i.e. hypoglycemic unawareness, should be excluded from trials where the glucose lowering capabilities of new compounds are not yet completely defined. While predominantly a clinical problem recognized in patients with type 1 diabetes, hypoglycemia unawareness with impaired counterregulatory responses may affect patients with type 2 diabetes of long duration.

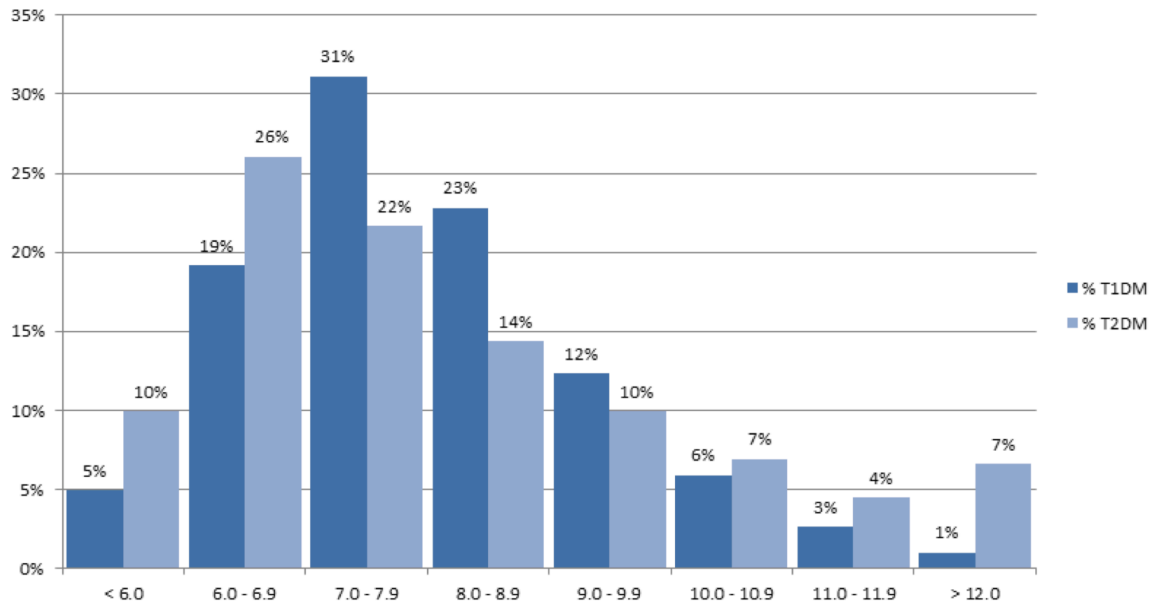

Figure 1. HbA_{1c} distribution derived from a subset of US patient volunteers with type 1 diabetes (n=874, 53% of total population) or type 2 diabetes (n=2889, 33% of total population) for whom clinic-measured HbA_{1c} results were available. About 1/4 of volunteers with type 1 diabetes had an HbA_{1c} of <7.0% (<53 mmol/mol) and about 1/3of volunteers with type 2 diabetes were similarly well-controlled. Data on file ProSciento, Inc.

Comorbidities

The presence of comorbidities that might pose a risk in administering the investigational agent to the subject or confound the results of the trial may make some patients poor study subjects. Patients with type 2 diabetes are at elevated risk of prevalent cardiovascular disease, autonomic neuropathy, fatty liver disease, proliferative retinopathy, nephropathy, the metabolic syndrome, sleep apnea, and depression. Older adults with diabetes may have age-related comorbidities including cognitive impairment, degenerative joint disease or frailty syndrome. While patients

with comorbidities may be more representative of the target population they can also be at increased levels of risk when participating in studies of novel drugs (Table 1). Furthermore, the disease state and associated long-term complications – notably compromised renal or hepatic function – may impair drug absorption, metabolism, or excretion, which could have an impact on initial assessments of drug pharmacokinetics and pharmacodynamics.

Of particular importance in adults with type 2 diabetes is atherosclerotic coronary artery disease. If screening with a careful medical history and a 12-lead electrocardiograph suggest undiagnosed clinically significant disease further evaluation is required. While a history of a cardiac event does not invariably lead to exclusion from participation in early phase trials, such individuals should be excluded from first-in-human studies until there is a greater understanding of the risk associated with exposure to the compound under development. Persistent blood pressure >160 mmHg systolic and >95 mmHg diastolic is exclusionary in most trials, and should prompt referral of the patient to a physician for further assessment.

Table 1: Considerations and associated risks when selecting patients with type 2 diabetes for early phase clinical trials

	Exclusion Criteria	Risks
HbA_{1c}	HbA_{1c} below a lower limit of 6.5% or 7% (48-53 mmol/mol) and above an upper limit of 10-11% (86-97 mmol/mol)	Hypoglycemia, if HbA_{1c} is normal or only modestly elevated; unacceptable hyperglycemia, if HbA_{1c} is above the upper limit
Hypoglycemia	Medical history of recent and/ or recurrent bouts of hypoglycemia	Hypoglycemic unawareness
Atherosclerotic coronary heart disease	QT/QTc interval according to ICH E14 clinical guidance	Cardiovascular disease
Fatty liver disease	Serum transaminases > 3X upper limit of normal	Liver disease
Diabetic nephropathy	Poor renal function based on the eGFR calculated by the MDRD	Deterioration of renal function with increased risk of iatrogenic hypoglycemia
Hypertension	>160 mmHg systolic and >95 mmHg diastolic	Cardiovascular complications
Dyslipidemia	Triglyceride levels >4.5 or 5.1 mmol/L (>400 or 450 mg/dL)	Acute pancreatitis

eGFR: estimated glomerular filtration rate; ICH: International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use; MDRD: Modification of Diet in Renal Disease

Concomitant Medications

Patients whose diabetes is well controlled with diet and exercise are the preferred participants for first-in-human or single ascending dose and multiple ascending dose studies. However, the majority of potential trial participants use prescription (e.g., glucose-lowering agents [most commonly metformin], antihypertensive drugs, lipid modifying agents [statins and fibrates], antidepressants [serotonin reuptake inhibitors] and aspirin) or over-the-counter medications. These should be restricted in early phase clinical trials if information regarding drug-drug interactions with the investigational agent is limited. If interventional agents are being developed as add-on therapy to metformin, the maintenance of metformin monotherapy should be included in the study protocol. When used either as primary prevention of cardiovascular disease, and especially in patients with a history of known coronary heart disease, statins may be continued during a trial as background therapy. Otherwise, a wash-off period that takes into account the half-life and pharmacodynamics of the medication(s) and safety parameters defining criteria for discontinuing a subject from the study and returning them to their pre-trial medication are essential.

Patients with Type 1 Diabetes

Patients with type 1 diabetes tend to be younger than those with type 2 diabetes, although there is considerable overlap. Type 1 diabetes is unlikely to be accompanied by major tissue complications or important comorbidities unless diabetes has been present for many years. Hypoglycemia unawareness is associated with longer duration of diabetes and lower HbA1c levels.

Management of Patient Populations at Study Sites

Once included in early phase clinical trials, patient populations may require special management at study centers. For patients with type 2 diabetes, ongoing and careful evaluation for cardiovascular disease is essential. For obese patients, plans to access equipment that can accommodate larger subjects may be necessary. Special beds may be required for overnight stays and additional consideration is needed to ensure available bathroom facilities are comfortable. Weight maintenance is essential where weight loss is a primary or secondary objective. Patients with degenerative joint disease may have mobility issues and need special accommodations to manage their disabilities. Patients with sleep apnea may require continuous positive airway pressure or other support, assuming that the therapy is compatible with the protocol.

Special Populations

In some circumstances, safe and ethical inclusion of patients with special characteristics, such as those in the pediatric and adolescent age groups and women of childbearing potential, in early phase clinical trials may be required. This mandates specific risk management strategies. Research with pediatric and adolescent populations should be performed at centers with special expertise and the resources to manage children and their parents or guardians. Most early clinical development programs exclude women of childbearing potential because of concerns around accidental fetal exposure if pregnancy occurs during study treatment. Participation is occasionally allowed with extreme precautions to avoid pregnancy.

Conclusions

Patients with the disease of interest are increasingly enrolled in clinical trials. This is an increasing trend in trials of new drugs for diabetes. Careful consideration of the risks, benefits and practical challenges of studying patients with disorders of carbohydrate metabolism are required. Although inclusion/exclusion criteria will inevitably eliminate some patient volunteers, appropriately conducted early phase clinical trials in patients with stable diabetes can accelerate the movement of viable and safe drugs into later phases of development.

Looking Ahead

The development of new therapeutic compounds is associated with challenges, such as increasing costs, strict regulations, and global competition, it is essential to optimize drug development programs. Improved strategies for implementing efficient recruitment of targeted populations for early phase clinical trials will shorten drug development timelines. Currently, most early phase diabetes-related trials include relatively small numbers of patients, are primarily conducted at single sites, and are of fairly short duration. In the future, diabetes-related trials should be expanded to investigate the effects of new therapies in diverse high-risk and representative populations, including children and elderly participants and those at risk for cardiovascular events. There is also a need for the benefits and risks of multiple therapeutic options for diabetes and other diseases to be evaluated in comparative effectiveness trials. As the size and complexity of early phase studies increase the management and safety of the study populations will require careful consideration. Recruiting and retaining subjects with diabetes and those with additional special characteristics in early phase clinical trials will create a reliable evidence base for clinical care guidelines and ensure safe and effective clinical interventions for these patient groups.

Further Reading

Dresser, R. First-in-Human Trial Participants: Not a Vulnerable Population, but Vulnerable Nonetheless Law Med Ethics 2009; 37(1): 38–50.

Kahn, S.E., Cooper, M.E., Del Prato, S. Pathophysiology and Treatment of Type 2 Diabetes: Perspectives on the Past, Present, and Future. Lancet 2014; 383(9922): p. 1068-83.

Krentz AJ, Morrow L, Hompesch M. Developing New Drugs for Diabetes and Cardiometabolic Disorders: A Changing Paradigm. Drugs 2012; 72 (13): 1709-1711.

Krentz AJ, Morrow L. Early phase metabolic research with reference to special populations. In: Krentz AJ, Heinemann L, Hompesch M. Translational Research Methods for Diabetes, Obesity, and Cardiometabolic Drug Development: Focus on Early Phase Studies. Springer 2015.

UKPDS Study Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998;352:854-64.

Yang F, Stewart M, Ye J, DeMets D. Type 2 Diabetes Mellitus Development Programs in the New Regulatory Environment with Cardiovascular Safety Requirements. Diabetes Metab Syndr Obes.Diabetes 2015; 8:315-325

Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. 2015;373:2117-28.

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Dr. Morrow's career in clinical research and experimental studies for insulin resistance, diabetes mellitus, and carbohydrate metabolism spans more than 20 years. As Chief Operating Officer, she leads the clinical operations and project management teams at ProSciento and has acted as principal investigator for more than 80 clinical research studies for metabolic small and large molecule therapies, biologics, biosimilars, and devices. Dr. Morrow is an author on more than 50 publications, including peer-reviewed journals, textbook chapters, and invited editorials.

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