INTERNATIONAL CONSORTIUM for INNOVATION & QUALITY in PHARMACEUTICAL DEVELOPMENT

Roadmap to 2030 for New Drug Evaluation in Older Adults – View of Pharmaceutical Industry

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Industrial Perspective – Big Picture Themes

- Ideal - Information obtained during development, not post-approval
- Tools: M&S and Stats techniques to examine PK, PK/PD, Efficacy and Safety
- Current state: ~30% of clinical trial participants are ≥65
  - Is it age or something else?

"The topic of the Elderly is not new"...(has been under discussion since 1987)

…the observations made during clinical trials that include both younger and older patients, if properly analyzed and particularly if accompanied by blood level data for each patient, should allow detection of important pharmacodynamic differences related to age or other influences. (Temple R., Clin Pharmacol Ther 1987)

<u>Last year 2020 draft guidelines:</u>

- Geriatric Information in Human Prescription Drug and Biological Product Labeling;
- Inclusion of Older Adults in Cancer Clinical Trials;
- Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs

What is the problem?

The general questions

- Do early stage clinical programs generate sufficient data to inform dose selection in geriatric patients in late stage development?
- Does the efficacy and safety demonstrated in clin development program, in particular in pivotal phase III studies reflect effectiveness and safety in a geriatric population?
- Are we able to define the right dose for a geriatric population based on our clin development program at the time of submission?

What keeps us form getting the data?
Is elderly participation restricted based on age?

Database: ClinicalTrials.gov

Searched for:

- Studies started: 1/1/2010 to 12/31/2021
- Not pediatric only
- Phase 3
- Industry Sponsored

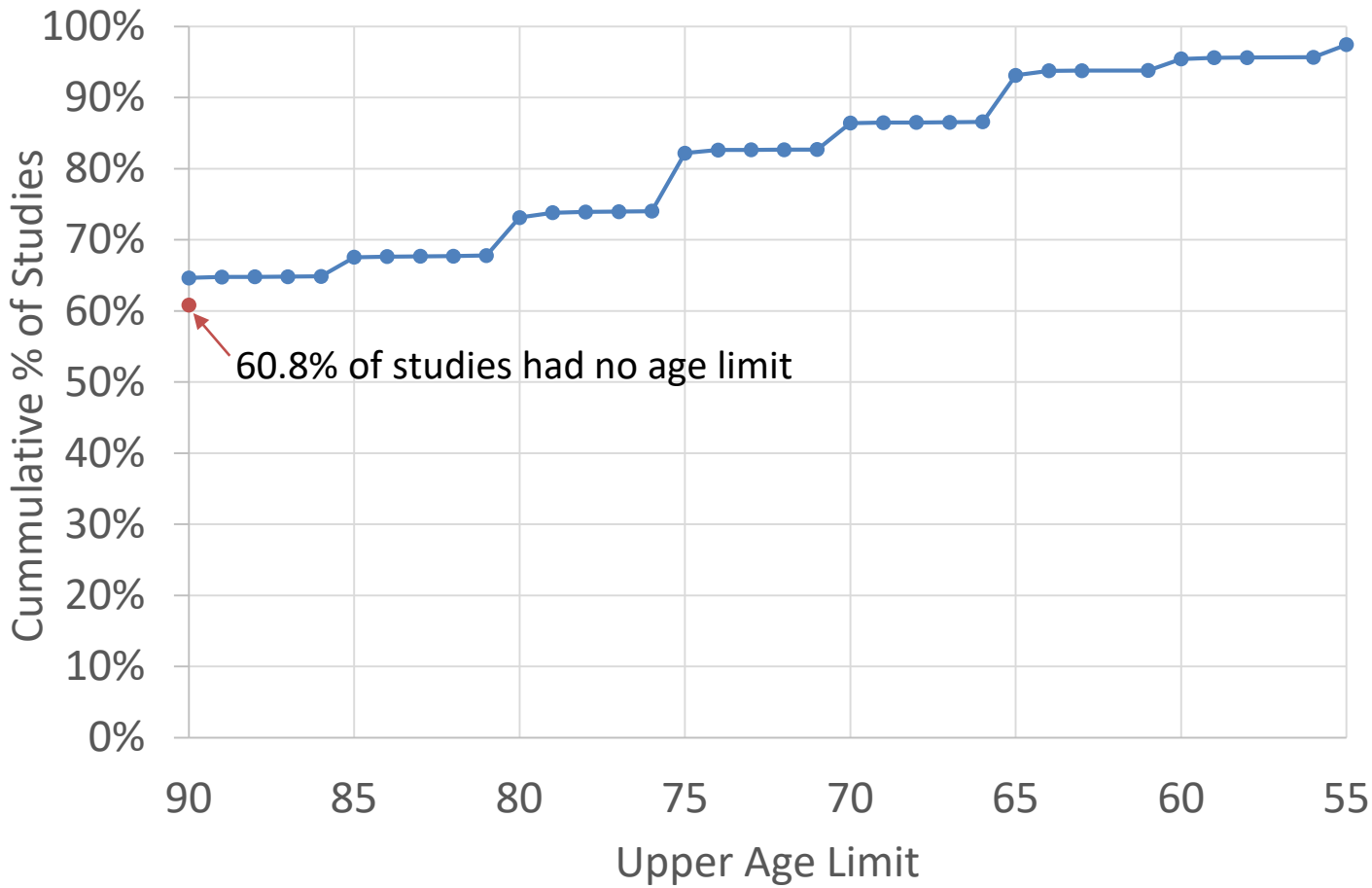
❖10,676 studies found

Further restrictions:

- Downloaded top 10,000
- Eliminated studies:
  - Upper age limit ≤18 years
  - Total enrollment <50

❖8702 studies used

Majority of studies allow “elderly”



- 1.6% of studies had an upper age <55
- 1.0% of studies had no defined limits listed

Trivia

- 1.7% of studies had an upper limit ≥100 (range was 100 to 130 years)

- Conclusion – **Age I/E criteria may not be the problem, rather the problem may be with other hurdles for participation**

Ad hoc survey on controlled registration trials (Among WG Members)

Number of trials: 51. Indications: Onc, CV/Metabolism, Resp/Immun/Inflamm, ID, Osteoporosis, AD

Age restriction per protocol:

- None/Adult: 38 (74%)
- Dedicated older adult: 5 (≥70 years; ≥65 years, ≥75 years, ≥40 years),
- Adult age ceiling: 8 (≤80 years, <99 years, <75 years)

Actual age range: 44 (86%) report patients ≥ 75 years

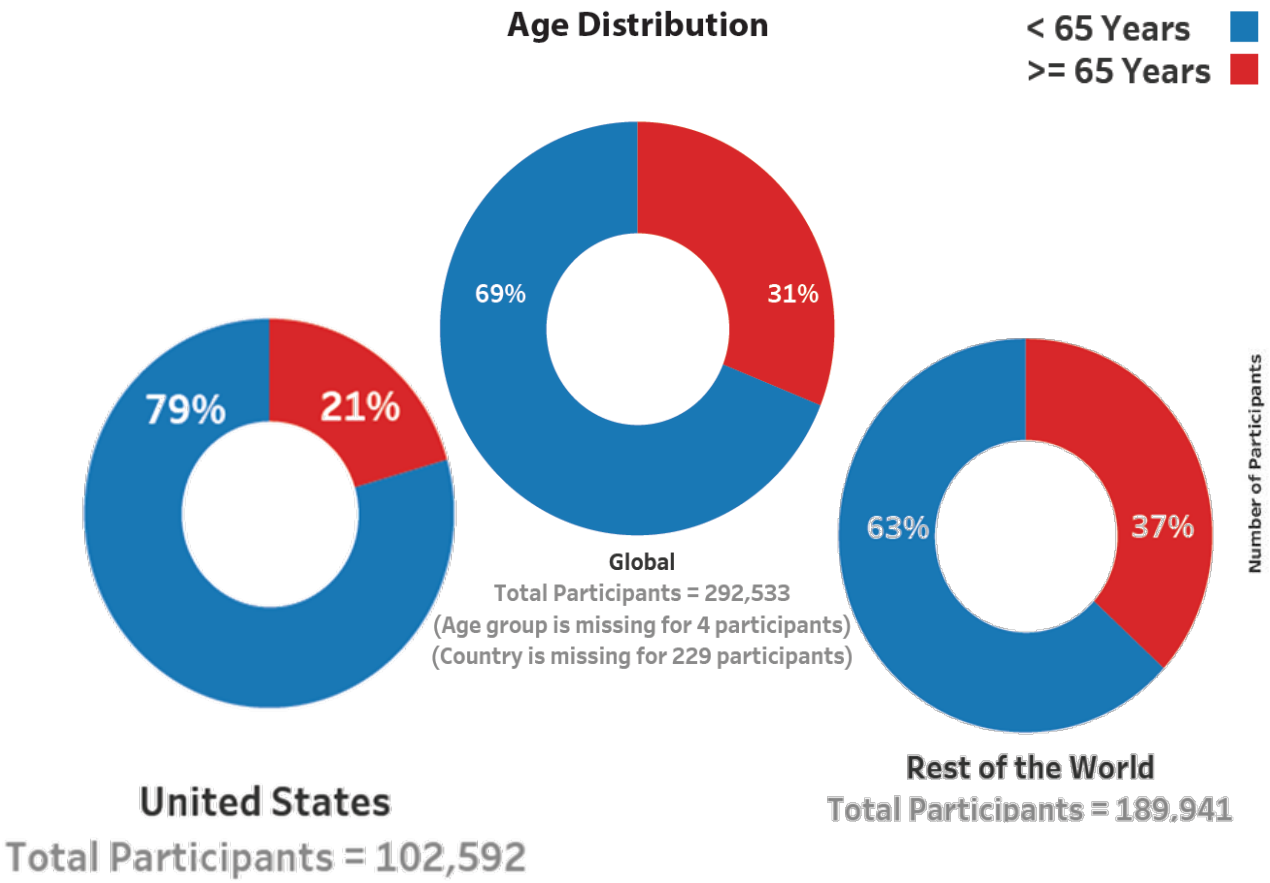
Additional design features to increase inclusion of elderly: 2 (broader co-morbidity and co-medication inclusion)

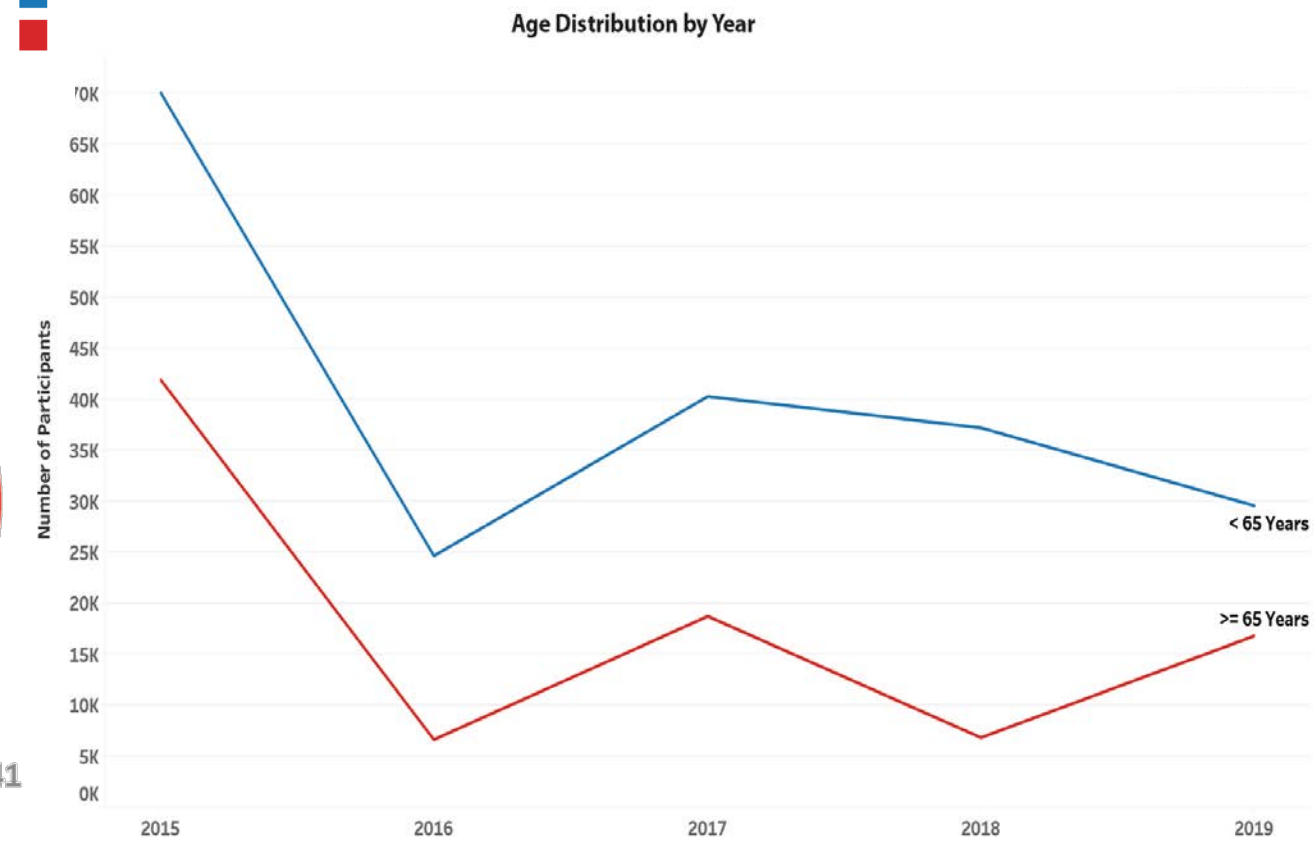
Age related dosing recommendation: 1 excludes age > 75 years

PopPK applied: 32 (Other modeling: ER 12, QSP/Disease Progression 6, PBPK 1)

FDA Drug Trials Snapshot Summary Report 2015-2019[1]

Overall, the majority of trial participants were younger than 65 years of age.
On average, participants in the U.S. tended to be younger than those in the rest of the world.





1. FDA. 2019 Drug Trial Snapshot Summary Report. https://www.fda.gov/media/135337/download
2. Meola A. The aging US population is creating many problems—especially regarding elderly healthcare issues. Business Insider. Jan 19, 2021, https://www.businessinsider.com/aging-population-healthcare

Is it a PK issue or …?

Is PK an issue?

General more frequent organ impairment (renal- and hepatic impairment)

General change in blood flow, liver size; changes in serum protein composition (chronic inflammation)[1,2] and body composition, increased gastric pH and delayed gastric emptying[1]

The major liver enzymes (e.g. CYP3A4) [3,4,5,6] and DDI effect mostly preserved in elderly[7]

Some transporter action may decline[8]

Increased IIV in a geriatric population by multiple factors[9]

The factors are mostly known, can be addressed in clinical development and by modeling tools (e.g. PBPK, PopPK) but age is not completely reflecting intrinsic factors (organ impairment) and not external factors (compliance, comedication)

[1]Klotz, U, Drug Metabol Rev 2009, 41:2, 67-76; [2]Morgan, E.T., Clin Pharm Ther 2009, 85, 434–438; [3]McLachlan A. & Pont LG., J Gerontol A Biol Sci Med Sci. 2012, 67A:175–180; [4]Gorski JC. et al., Clin Pharm Ther 2003,74:275-87; [5]Schwartz JB., Clin Pharmacol Ther 2006;79:440-8; [6]Parkinson A. et al., Toxicol Appl Pharmacol 2004, 199: 193-209; [7]Stader et al., Clin Pharm Ther 2021, 109: 471- 484; [8]Bauer et al., Clin Pharm Ther accepted September 8, 2020 doi:10.1002/cpt.2052 09; [9]Magoni AA & Jackson SHD, Br J Clin Pharm 2004, 57: 6-14

Chronological Age as Denominator?

Age of ≥ 65 years? *Arbitrary based on age to define participation of pension plan by German chancelor Bismarck from end of 19th century*.

Additional Age Categories: >75, > 80 and > 85 years ?[1]

Use of Frailty Index ?[2] Frailty index may help to identify patients susceptible to more harmful Aes (fall as result of dizziness

- Short Physical Performance Battery (SPPB) and Gait speed

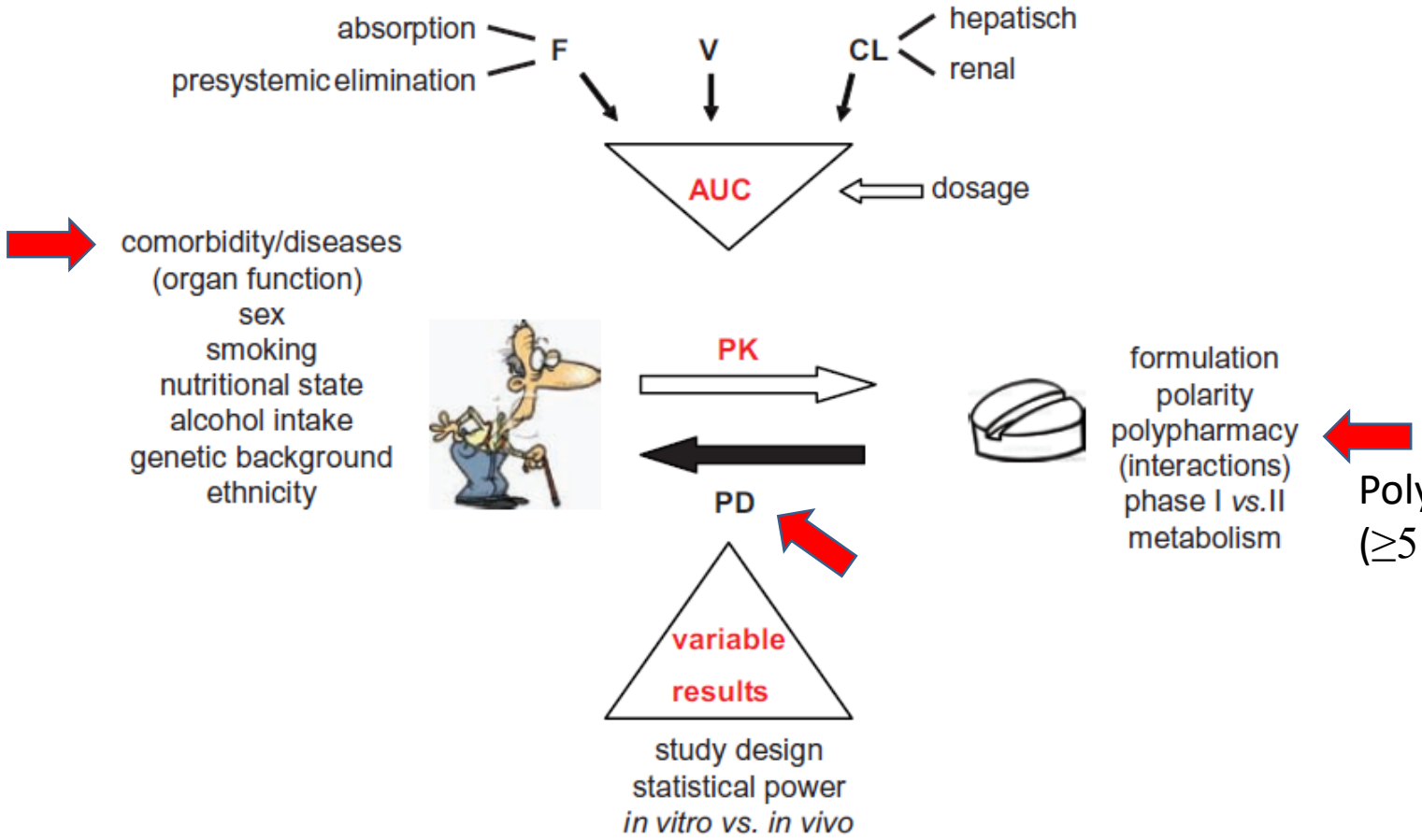
Consideration of cognitive impairment, separate from frailty?[3]

Biological age based on markers, e.g. clearance processes (probes, renal CL) or DNA methylation patterns? [4]

Neither Age nor Frailty and probably not "biological age" is completely reflective of the underlying issues: multimorbidity, polypharmacy, deviating PD and more harmful AEs.

[1] Guidance for industry E7 Studies in Support of Special Populations: Geriatrics: Questions and Answers; [2] Geriatric Expert Group Reflection paper on physical frailty adopted (europa.eu);[3] Surr CA, et al. J Geriatr Onco 2020, 11: 1125-32; [4]Dücker & Brockmöller Clin Pharm Ther 2019, 105: 625-640

The real gap: PD, effectiveness, safety similarity (more harmful AEs), co-morbidities and polypharmacy



Polypharmacy due to co morbidties (≥5 drugs in > 30% in > 65 years[1])

[1]Quato, D. et all. Changes in Prescription and Over-the-Counter Medication and Dietary Supplement Use Among Older Adults in the United States, 2005 vs 2011. JAMA Intern Med. 2016;176(4):473-482.

Figure adapted from Klotz, U. , Drug Metabol Rev 2009, 41:2, 67-76

Can we use Real World Evidence?

Example: disease predominantly in a geriatric population DOACs (Apixaban, Dabigatran, Rivaroxaban) in stroke prevention in nonvalvular atrial fibrillation

Large phase III trials with substantial contribution of elderly (average age >70, between 31 – 40% > 75 years) – PopPK, E-R and also PBPK applied

Stroke risk and bleeding risk depending on age but only two compounds labeled with age adapted dosing:

- Dabigatran in EU, Canada and Japan (*for* $\geq 80, >75$ *and* > 70*years*) and Apixaban as composite (*patients with at least 2 of the following characteristics: age* $\geq$ *80 years, body weight* $\leq$ *60 kg, or serum creatinine* $\geq$ *1.5 mg/dL*)

Retrospective Analysis per EMA Procedure under Article 5(3) of Regulation (EC) No 726/2004 (Assessment report EMA/194375/2020) – Focus on bleeding:

- Analysis including a total of 421,523 (mainly elderly) patients from EU and Canada and additional US based data from in total 448,944 Patients (Graham et al., 2019):

generally higher risk of bleeding among DOAC users aged >75 years is in line with the results from the pivotal studies... these data were not sufficient to recommend dosage changes in this population

Further Examples on RWE compared with RCTs – not predominantely geriatric population

- Diabetes – EU-IMI: *GetReal Initiative* (Ankarfeldt M, et al., Clin Epidemiol. 2017 Jan 23; 9:41-5)
  - no efficacy–effectiveness gap was observed and no drivers of effectiveness were identified

- Oncology- Hodgkin‘s Lymphoma from *EU PICOS-T framework* (PICOS framework + T for time horizon)
  - efficacy effectiveness gap was that older patients are often excluded from trials (33% exclude patients >65 years and 39% exclude patients >70 years)
  - Age was also found to be the most important driver of effectiveness – it was associated with shorter progression-free and overall survival, and less aggressive treatment due to comorbidities and physician reluctance. Age is also associated with two other important drivers of effectiveness: comorbidities and severe side effects

Value of RWE to improve therapy in elderly patients?

RWE may not add much information on effectiveness:

- when substantial portion of pivotal phase III patients were elderly
- the disease and PD does not change with age
- data are too insensitive to define a dose or posology

RWE can be helpful to:

- Generate additional info when phase III does not generate sufficent elderly data (e.g. certain oncology indications)
- Detect rare safety events post approval
- Generate information on common co-morbidities, common standard of care and co-medication **to be used during clinical development**

RWE may be more applicable as new approaches are considered:

- Can be used for new statistical approaches such as *propensity score-integrated power prior* approach or *inverse propensity score reweighting* methodology to estimate the expected treatment benefit if a clinical trial had been run in a broader real-world target population (*Wang C., et al., 2019; Happich M., et al., 2020*)
- New pragmatic trial designs such as *Cohort Multiple Randomised Controlled Trial* design (*Pate A., et al., 2006*)

Summary and Outlook

Summary

Inclusion of elderly in clinical trials

- Age restrictions per protocol are the exception
- Share of older adult patients in clin development programs relatively constant over the years and dependent on disease area
- Actual inclusion of older adult population may be hampered more by other in- or exclusion criteria, screeening failures and other factors like lack of information about a trial, mistrust of older adults, problems with informed consent (need of caregiver; cognitive impairment not well addressed) and limited mobility

PK in the elderly

- General age related PK changes are mostly understood and modeling approaches can be employed
- Age related dosing recommendations are not common. Dosing adaptations more common on other factors (organ impairment, co-meds)

Summary (cont)

Age as a predictor

- Chronological age as category sufficient for trial design and may partly reflect different PD (longer disease progression, more severe AEs) but is only partly reflecting the underlying issues of age related higher incidicence of co-morbidities and polypharmacy.

Real World Evidence

- Extrapolation from younger to older adults may be possible in some indications (Diabetes) while in some considered difficult (oncology)
- Real World Data post approval are of limited use for dose definition but may detect efficacy-effectiveness gaps or new safety findings
- Real World Data pre-approval can help to better define the target population and address common co-morbidity and DDIs and may allow new stats methods and trial designs

Outlook

- Age related information to be preferably generated pre-approval; best to plan how one will obtain that information in advance rather than expecting it to appear at the end[1]
- Adult older population is often large part of the target population. It will be in the sponsor‘s interest to include these patients and may not need an additional incentive/penalty framework
- Unlike the peditaric situation no scarcity of patients
- Whenever feasible inclusion of older adult population in pivotal trials in a proportion more resembling the real world situation; **How to raise awareness and reduce barriers to facilitate participation of older adults in clinical trials?**
- Innovative,more pragmatic trial designs may be an option (home centered, digital, less complex, enrichment, Cohort Multiple Randomised Controlled Trial)
- Application of modeling (PopPK, E-R, QSP, PBPK-PD) in combination with statistical approaches (PS / Bayesian borrowing) will be further evaluated

[1]Powell JR, Cook J, Wang Y, Peck R, Weiner D. Drug Dosing Recommendations for All Patients: A Roadmap for Change. Clin Pharmacol Ther. 2020 May 26. doi: 10.1002/cpt.1923. Epub ahead of print. PMID: 32453862.