**Table 3.** FDA (2015) and EMA (2012) guidance on complicated urinary tract infections (cUTI) trials in adults and proposal for study design in febrile UTI clinical trials in children

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| **Study design** | **EMA 14** | **FDA 13** | **Proposal** |
| Inclusion criteria | a) indwelling urethral catheter, urinary retention, urinary obstruction, neurogenic bladderb) minimum number of signs of systemic upset and one or more of flank or pelvic pain, tenderness in the costo-verterbral area, fever, dysuria, frequency or urgencyc) pyuria ≥10 WBCs/mm3 d) colonies > 105 CFU/mL of single pathogen | - cUTI and one of: indwelling urinary catheter, urinary retention, neurogenic bladder, obstructive uropathy, azotaemiaOR - pyelonephritis and patients with normal urinary tract anatomyAND at least two: chills or rigors or warmth associated with fever , flank pain (pyelonephritis) or pelvic pain (cUTI), nausea or vomiting, dysuria, urinary frequency or urgency, costo-vertebral angle tendernessAND dipstick positive for leukocyte esterase or ≥ 10 WBC/mm3 | - Abnormal urinary dipstick test (leucocyte esterase >1+, or nitrite positive) **OR** - urinalysis (≥5 white blood cells per high power field in centrifuged urine or ≥10 white blood cells per mm3 in uncentrifuged urine, and bacteriuria with any bacteria per high power field) **AND**at least two of the following clinical or biological signs: (1) fever with temperature of 38°C or higher(2) general, non-specific signs such as irritability, vomiting, diarrhea, or feeding problems for children < 2 years abdominal or flank pain, urgency, frequency, dysuria, suprapubic tenderness for children > 2 years(3) C reactive protein OR procalcitonin concentrations elevated according to the local laboratory**AND** - positive urine culture with no more than two species of microorganisms:* spontaneously voided urine with ≥ 105 microorganisms per ml of urine **OR**
* suprapubic aspirate/urinary catheter with ≥ 104 microorganisms per ml of urine

**OR**- positive blood culture **AND** no other recognized cause. |
| Exclusion criteria | a) ileal loops or vesico-ureteral refluxb) signs and symptoms suggesting prostatitis | a) any recent antibiotic use (e.g., within 48 h of enrolment) that could affect the treatment of UTI b) concurrent use of non-study antibacterial drug with potential effect on outcome evaluationsc) suspected or confirmed prostatitis d) renal transplantation e) ileal loops f) patients who are likely to receive or on-going antibacterial drug prophylaxis after treatment g) recent history of pelvic/urinary tract traumah) indwelling urinary catheters expected to remain in place after therapy has been completed i) uncomplicated UTI | a) known allergy to study drugsb) major underlying conditions (known UT abnormalities, chronic disease immunodeficiency, shock)c) Recent infection (the last 7 days) or antibiotic course (the last 48 hours) |
| Primary Endpoints | microbiological success: < 103 CFU/mL, documented at TOC visit 7 days after end of treatmentANDresolution of UTI-related clinical signs/symptoms | a) outcome for IV drug therapy at day 5: - positive clinical response (resolution of presenting symptoms and no new symptoms) and microbiological success - clinical or microbiologic failure: no complete resolution of symptoms at presentation or new symptoms, or death, or growth ≥ 104 CFU/mL of original pathogen (during or after treatment)b) efficacy assessment at day 7 d after treatment for trials using the same duration of antibacterial drug therapy in both treatment groups | a) concomitant clinical and microbiological evaluation for the on antibiotic-therapy (OAT) and the test of cure (TOC)b) OAT: 48h-72h after the beginning of antibiotic therapy and TOC: 5 to 7 days after the end of treatmentc) clinical cure defined as defervescenced) microbiological cure defined as urine sterilization (if positive urine culture: assess the antibiotic susceptibilities) |
| Secondary Endpoints |  | evaluation for continued resolution of symptoms and microbiological success at a fixed time point approximately 21 to 28 days after randomization | concomitant clinical and microbiological evaluation 14 to 21 days after EOT (relapse/recurrence/reinfection) with assessment of the antibiotic susceptibility of the new isolate in case of positive urine culture |