ADVERSE EVENT MONITORING

AND

ADJUNCTIVE SERVICES AND ATTRITION PREVENTION (ASAP)

IN THE

NIMH TREATMENT OF ADOLESCENT DEPRESSION STUDY (TADS)

AE/ASAP Manual: Final Version (4.1)

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Overview

To ensure patient safety and to evaluate the tolerability of treatment, TADS will require careful monitoring of: (1) affective disorder symptoms, (2) adverse events, (3) concomitant medications and (4) out-of-protocol interventions. To this end, this manual has been developed to delineate and standardize procedures for **Adverse Events Monitoring** and **Adjunctive Services and Attrition Prevention** that will be necessary to address those clinical crises and concerns that inevitably will arise in the course of treatment during the NIMH Treatment for Adolescents with Depression Study (TADS). To balance feasibility with our need to gather important information, TADS stays carefully centered between the FDA regulatory approach (record everything) and need to minimize subject and investigator burden.

Definitions

Adverse Event

An adverse event is defined as any unfavorable medical change that occurs during or after beginning the study that may or may not be related to or caused by study drug or CBT treatments. A medical event is defined as a clinically significant change in physical and/or mental health status.

Adverse events include the following:

1. Any medical event that causes clinically significant interference with functioning (e.g. headache that causes school absence or otherwise causes clinically significant activity restriction).
2. Any event that requires medical attention, e.g. a URI with visit to a doctor.

Adverse events do not include the following:

1. Any medical event that induces the subject to take a concomitant medication (e.g., URI that causes the subject to take an over the counter decongestant) unless that event also satisfies AE criterion 1 or 2 above. For example, a headache for which the subject took Tylenol would not be defined as an AE unless it also prompted him/her to miss school or go to the doctor.
2. Behavior change, such as simple truancy, that is not directly attributable to a change in mental health, e.g. truancy secondary to mania.
3. AE reporting does NOT include pre-existing conditions or illnesses that do not worsen or increase in frequency during the study period.
4. AE reporting does not include doctor visits for routine medical care, prescription renewals, immunizations or routine dental or other preventive care.

As noted below, concomitant treatments are documented on the Concomitant Mental Health Treatment Log (CTL) or Concomitant Medication Log (CML) not on the Adverse Event Form (AEF). The CTL documents all outside-of-protocol mental health or psychiatric medication and non-medication treatments that the teen received, while the CML is used to record medication taken outside of the protocol for non-mental health reasons.

Adverse events may or may not trigger ASAP procedures, with the distinction turning on whether the site makes the determination under ASAP rules that out-of-protocol interventions are required to manage the AE.

Subject-Initiated Protocol Violations

If it is discovered during or after the study that a subject actually received a "cross-treatment" on his/her own (e.g., a parent reveals that an adolescent in the CBT-only group received fluoxetine from his or her private physician during the study), we will document the cross-treatment in the clinical record, the Concomitant Mental Health Treatment Log (CTL) and, for later analysis, the CASA. While TADS staff is expected to strongly discourage treatment outside the study, these subjects would continue to be treated within their assigned treatment arm. Stated differently, **subject initiated protocol violations do not trigger AE or monitoring or ASAP unless indications for AE monitoring and/or for ASAP are present**.

Subjects receiving cross-arm treatments on their own accord, e.g. that are not initiated under ASAP, are not automatically considered premature terminators. On the other hand, subject-initiated cross-arm treatment should prompt consideration of whether (1) ASAP procedures are necessary and/or (2) premature termination under ASAP is in fact warranted by the subject's clinical status.

Premature Termination

At any time during Stages I, II or III, subjects may deteriorate or develop clinical crises that lead the TADS site team to recommend termination or modification of the study treatment (but almost never the assessment) portion of the protocol. For example, a subject who became psychotically depressed, suicidal or manic and required hospitalization would almost certainly require open clinical treatment under emergent ASAP rules. Other subjects will continue in TADS treatments *and* will require treatment outside the study as determined under elective ASAP procedures. All such subjects should continue in their assigned arms insofar as possible. For example, medication-only subjects who had been given CBT treatment under ASAP procedures would continue to receive the medication treatment according to protocol; CBT-only subjects who had been referred for medication by the treatment team under ASAP procedures would continue to receive as much of the CBT treatment as possible. Such patients will be considered "premature terminators." These are equivalent to "investigator-initiated protocol violators." "Prematurely terminated" subjects may continue to be treated within their assigned treatment arm (as long as this does not pose a danger of contaminating the treatment of other subjects in that arm) and we would continue to collect assessments throughout the remainder of their scheduled time in the study.

"Drop Outs"

Subjects who terminate prematurely are to be distinguished from "drop outs" that are defined as subjects who refuse to furnish further data. Stated differently, dropouts are defined as those subjects who withdraw consent from the assessment portion of the study. Subjects who drop out are not eligible for TADS treatment. A subject who drops out should be encouraged to return for a last major (or, failing that, a minor assessment), which would then be followed by end-of-treatment recommendations.

Affective Disorders Monitoring

At each visit (except parent only CBT sessions) all subjects will complete an Affective Disorders Screen (ADS) that will serve as the basis for review by each clinician (pharmacotherapist and CBT therapist) of the subject's clinical status with respect to his or her affective illness. The ADS is modeled on the CDRS for MDD and the Young Mania Rating Scale (YMRS) for hypomania and mania. The patient portion of the ADS will use a dichotomous outcome (Symptom present, Yes/No); the clinician will then score on a 0-3 point scale as absent, mild (present, no interference), moderate (present, some interference), severe (present, major interference). This data, which will be transmitted to the CC for scoring, will be used to guide appropriate clinical care. **Either mania or worsening MDD may trigger ASAP; only mania is considered an AE, however.**

Further information on the ADS is available in the Clinician Assessment Manual.

Timing of Assessments

At the point of premature termination or "dropping out" an additional major assessment battery will be obtained unless the last major assessment battery had been obtained within the prior month. If the next scheduled full assessment is due within 1 month of this "early termination" assessment, that scheduled full assessment should be skipped. Patients who drop out should be reminded that they agreed to complete the assessment portion of the study and should be encouraged to complete a last minor assessment battery, or better, a last major assessment battery.

II. Adverse Event Monitoring

Patient Safety Monitoring

As shown in **Table 1**, TADS uses one patient form, five clinician forms and one summary form to monitor patient safety. The patient form is an Affective Disorders Screen (ADS). The site forms are an Adverse Event Form (AEF), a Serious Adverse Event Form (SAE) a Concomitant Medication Log (CML), a Concomitant Mental Health Treatment Log (CTL), and an ASAP Form (ASAP). Drawing on these forms, the Patient Safety Monitoring Log (PSML) is a summary form that is used to track adverse events, serious adverse events and/or ASAP over time for purposes of reporting to the TADS Data Safety and Monitoring Board and as a tool for sites and the Coordinating Center to use for overall patient monitoring. Specifically, in the event of an AE, SAE or ASAP indication, the therapist/SC complete the appropriate form (AEF, SAE, ASAP) and record the event in summary fashion on the PSML.

- The Affective Disorders Screen (ADS) inventories affective disorder symptoms.
- The Concomitant Medication Log (CML) inventories concomitant medications taken for non-mental health reasons.
- The Concomitant Treatment Log (CTL) inventories concomitant medications and non-medication interventions received for mental health reasons.
- The Adverse Event Form (AEF) inventories adverse events.

- The Serious Adverse Event form (SAE) inventories serious adverse events.
- The Adjunctive Services and Attrition Prevention Log (ASAP) tracks the reasons and outcomes for ASAP.

Table 1: Patient Safety Measures*

Domain	Measure	Informant**	Who fills out form?
Affective Disorders	ADS	Patient	Patient / CBT or Pharmacotherapist every visit
Concomitant Mental Health Treatment Log	CTL	Patient /Parent	Study coordinator
Concomitant Medications	CML	Patient /Parent	Study coordinator
Adverse Events	AEF	Patient / Parent	Primary therapist
Serious Adverse Events	SAE	Patient / Parent	Primary Therapist
ASAP	ASAP	Clinician	Primary therapist / SC
Patient Safety Monitoring Log	PSML	Patient / Parent	Primary Therapist / SC

*See the TADS Suicide Manual for patient safety measures and procedures for managing suicidality.

**The ADS, , CML and CTL are filled out based on patient information, with input from the parent as needed. The AEF, SAE, ASAP Form require parental input.

Adverse Events

Using a separate AEF for each event, adverse events will be monitored identically across all treatment arms during Stages I, II, III but not Stage IV.

Specific principles for monitoring affective disorders, adverse events, concomitant medications, concomitant treatment and their relationship to ASAP are as follows:

Affective and other psychiatric disorders will be monitored using the ADS and general clinical inquiry. New onset psychiatric symptoms, such as emerging mania or panic attacks, will be recorded if they cause clinically significant interference with functioning as defined above. Symptoms of major depression will not be recorded on the AEF, but will be tracked on ASAP when ASAP procedures are recommended. For example, worsening MDD in a teen receiving CBT may result in a recommendation for medication by the TADS team under ASAP provisions, which in turn would be coded on the ASAP Form but not on the AEF.

At every visit, the treating clinician (CBT or pharmacotherapist in monotherapy conditions; pharmacotherapist for patients in COMB) will ask about any new health problems that caused the patient to alter his daily routine, seek medical care or take a new medication. The latter includes reviewing the CML and CTL, which the study coordinator will have completed with the

patient and parent prior to the visit with the clinician. Those events that meet AE criteria (listed above) will be recorded in the AEF.

Wherever possible, group classification, e.g. the flu rather than headache, fever and cough, will be used in preference to recording individual symptoms.

Not all adverse events, e.g. pneumonia, will initiate an ASAP intervention; not all ASAP interventions, e.g. withdrawal of consent, will occur in response to an AE. However, every event recorded on the AEF will specify whether or not an ASAP procedure was initiated in response to the AE. Every ASAP Form entry will specify whether the ASAP procedure involved an adverse event (recorded on the AEF) and serious adverse event (recorded on the SAE). All AEs, SAEs and ASAP events will be recorded on the PSML.

Withdrawal of consent (drop out) or premature termination will be recorded on the ASAP Form, not on the AEF.

Medication Side Effects

At each medication visit (office or phone) the pharmacotherapist will review the following:

- The previous AEF, PSML logs for unresolved events
- The current CML and CTL

The pharmacotherapist will then ask about medication side effects using the following general question: **"Any health or other problems this week?"** Having explored the nature of these problems, including potential medication side effects, the pharmacotherapist will complete an AEF only for those symptoms reported by the patient that met AE reporting criteria. On the AEF, the pharmacotherapist will then indicate his/her opinion as to whether the reported AE was medication related, the strength of this opinion and whether and what if any changes in medication (e.g. dose, timing) were made.

Concomitant Medication / Concomitant Mental Health Treatment Logs

At each treatment visit, the treating clinician (pharmacotherapist in all pills conditions or the CBT therapist in CBT) will review the CML and CTL, which the study coordinator will have completed with the parent and patient, recording intercurrent treatments on the AE, SAE or ASAP forms only if they meet criteria.

Physical Symptom Checklist

Patients will complete a self-report Physical Symptom Checklist (PSC) at baseline and at every assessment point throughout the trial. The PSC will use present/absent anytime in the past week. This data will **not** be used to guide clinical treatment or to trigger AE or ASAP reporting or action.

Suicidality

TADS procedures for managing suicidality are extensively discussed in the TADS Suicide Prevention Manual.

Serious Adverse Events

Any serious adverse event or death, <u>regardless of the circumstances or suspected cause,</u> must be reported immediately to Duke (for all subjects) and to Lilly Pharmaceuticals (subjects in pills

conditions only) if it occurs or comes to the attention of the investigator at any time during the study. Note that an SAE for a subject in a pills condition during Stage I requires breaking the blind to determine if the subject is taking PBO or FLX. Any SAE occurring at any other time after completion of the study must be promptly reported if a causal relationship to study drug is suspected.

A Serious Adverse Event (SAE), is defined by the FDA/Lilly as:

- Life threatening (at immediate risk of death)
- Requires hospitalization for any reason
- Results in persistent or significant disability or incapacity
- Results in congenital anomaly or birth defect
- Results in death
- Other significant medical event including cancer.

The only exception to the above reporting requirement is SAEs occurring during the screening phase prior to randomization.

Relationship of AE Reporting to ASAP

Types and indications for ASAP are as discussed below. The reason for ASAP referral, the decision of the ASAP Panel and the outcome of the ASAP intervention will be recorded on the ASAP Form. For each AE, the clinician will note on the AEF whether that AE triggered ASAP. If the answer is yes, then the ASAP Form should be completed. The type and outcome of the ASAP intervention will be specified on the ASAP Form.

Consistency of Records

It is the task of the study coordinator to review the AE, SAE, CML, CTL and ASAP records to make sure that they are consistent in "real time" so that clinical care of the patient does not suffer from lack of attention to AE/ASAP monitoring. Similarly, the SC will be responsible for completing the PSML to allow for real time adverse event monitoring by the Coordinating Center and pursuant to satisfying DSMB adverse event reporting requirements. At the point of data entry, the CC will also "flag" inconsistent records using standardized edit rules to generate queries to the site.

III. Overview of Adjunctive Services and Attrition Prevention (ASAP)

It is expected that most subjects will exit TADS treatments at Stage I (clinician-defined non-responders and PBO subjects) and at Stage III (completers). However, some patients may withdraw consent for treatment or both treatment and assessment (**drop out**). Others may suffer sufficient clinical deterioration from whatever source that the treatment team recommends that continuing TADS treatment is no longer appropriate or that additional out-of-protocol treatment is required (**premature termination**). Other patients/families may require out-of-protocol interventions during study entry or during Stage IV.

To meet these needs for out of protocol treatment, two ASAP sessions will be available during screening, four during Stages I and II, four during Stage III and 2 during Stage IV. **The number**

of ASAP sessions is stage specific, e.g. ASAP sessions cannot be carried over from one stage to the next.

A single ASAP session not from the "bank" of ASAP sessions noted above is available to manage dropping out. If threatened dropping out occurs on a second occasion, this ASAP session may be repeated once.

Finally, family members may require treatment outside the study. To insure cross-site consistency and excellent clinical care for TADS patients, these situations will be managed via ASAP procedures as specified in this ASAP manual.

Hence, there are 8 ASAP codes (settings requiring ASAP) each coupled to a specific set of allowable interventions. These involve ASAP during entry procedures, emergent and non-emergent clinical situations, ASAP during Stage IV, dropping out, and referral of family members for treatment outside TADS.

ASAP 1: ASAP During Entry

During the Gate B to C entry period, up to two ASAP sessions will be provided. Subjects in crisis at Gate A or between Gates A and B will be referred to community resources as appropriate. To avoid biasing post-randomization treatment, these ASAP sessions will involve assessment and supportive counseling without specific behavioral programming or treatment recommendations.

ASAP Indications 2, 3, 4, 5 During Stages I, II and III

It is expected that most subjects will exit TADS treatments at Stage I (clinician defined non-responders and PBO subjects) and at Stage III (completers). If necessary, however, ASAP provides consistent procedures for addressing two situations that may threaten a subject's full participation in TADS:

- Emergent clinical situations (site acts before ASAP Panel review) and non-emergent clinical situations (site requests ASAP intervention) affecting the welfare of the adolescent and his/her family.
- Situations potentially leading to premature termination.

Crossing these two exigencies, clinical emergencies and possible premature termination, generates the four situations detailed in **Table 2** that define the domain of ASAP during TADS Stages I, II and III.

Table 2: ASAP During Stages I, II and III

	Premature termination No	Premature termination Yes
No Clinical Emergency	**ASAP 2**: Non-emergent situation not leading to premature termination	**ASAP 3**: Non-emergent situation leading to premature termination
Clinical Emergency	**ASAP 4**: Emergency not leading to premature termination	**ASAP 5**: Emergency leading to premature termination

ASAP 2: At any time during Stages I, II or III, non-emergent clinical situations may develop that lead the TADS site team to recommend brief out-of-protocol interventions that do not lead to termination from the treatment or assessment portions of the protocol. For example, if family conflict interfered with a medication subject's willingness to complete an assessment point, the family could receive one or two family sessions from the study team under ASAP rules. If the situation did not resolve with a brief ASAP intervention because family conflict proved an enduring problem so that further treatment outside the protocol was required, then ASAP 3 applies.

ASAP 3: Other subjects will continue in TADS treatments but also will require elective treatment outside the study because of ongoing clinical situations that cannot be met within the framework of their TADS-assigned treatment or by using brief ASAP interventions. Such patients will be considered **"premature terminators"** and are equivalent to "investigator-initiated protocol violators." All such subjects continue in their assigned arms insofar as possible, e.g., prematurely terminated subjects may continue to be treated within their assigned treatment arm (as long as this does not pose a danger of contaminating the treatment of other subjects in that arm) and we would continue to collect assessments throughout the remainder of their scheduled time in the study. For example, medication-only subjects who had been recommended by the ASAP Panel for CBT treatment would continue to receive the medication treatment according to protocol, including monthly medication evaluations; CBT-only subjects who had been referred for medication by the treatment team under ASAP procedures would continue to receive as much of the CBT treatment as possible.

ASAP 4: Analogous to ASAP 2 but more emergent, some subjects will develop clinical situations that require immediate intervention without waiting for ASAP Panel approval. For example, a subject who developed acute school refusal because of panic attacks could receive brief clinical treatment from the study team under ASAP rules. If the crisis does not resolve and further treatment outside the protocol is required, then ASAP 5 applies.

ASAP 5: At any time during Stages I, II or III, subjects may develop clinical emergencies that lead the TADS site team to recommend emergent termination from the treatment (and sometimes the assessment) portion of the protocol. For example, a subject who became psychotically depressed, suicidal or manic and required hospitalization would almost by definition require open clinical treatment under emergent ASAP rules.

ASAP 6: ASAP During Stage IV

In Stage IV, two ASAP sessions will be provided for the purpose of crisis assessment and referral to appropriate community providers. No treatment will be provided during these sessions. However, to meet our ethical responsibilities to TADS patients and to assist with "sample maintenance," appropriate crisis/case management should be recommended as clinically appropriate outside the study.

ASAP 7: Dropouts

Some subjects may refuse participation in the treatment but not the assessment portion of the study. Such subjects are considered to be poorly compliant (come occasionally) or non-compliant (don't come at all) with treatment. **Subjects who decline treatment are not considered to have dropped out.** Subjects who are not compliant with treatment should be encouraged to continue in treatment by the primary therapist within the framework of the

assigned treatment, for example, by encouraging hopefulness about the eventual success of the medication or CBT intervention. Stated differently, a subject who is intermittently compliant with treatment should be managed within the customary treatment schedule. **Since poor or non-compliance by definition already involves an available open treatment session and is a common, perhaps even expectable, clinical issue, ASAP should be invoked only if there is a clear reason apart from poor compliance to initiate an ASAP procedure.**

Conversely, subjects who refuse participation in the assessment portion of the study are considered "drop outs." Subjects who drop out are not eligible for TADS treatment.

A single ASAP session in addition to the bank of ASAP sessions outlined above may be used to address the reasons why a family/patient may withdraw consent from the assessment portion of the study and to try to persuade, if possible, the family/patient to continue their participation. At a minimum, the parent or teenager should be encouraged to complete the major assessments even if the other will not do so, including a major assessment point at the point of dropping out.

This ASAP session, which is not to be used to address premature termination from treatment, may be repeated once and only once if a second instance of threatened dropping out arises.

ASAP 8: Referral of Family Members

Family members other than the teen may require referral for mental health evaluation or services during the course of TADS treatment for the identified patient. These are coded as ASAP 8, and listed on the ASAP Form. For example, maternal depression has been identified as a significant predictor of poor outcome in the treatment of pediatric MDD and should prompt referral (if possible) for clinical services outside TADS. Such a referral should be considered when the baseline BDI for either parent is > 20 and at any other point in the study when referral appears indicated on clinical grounds.

Note that in no instance should referral for treatment include treatment that overlaps TADS treatment, e.g. a referral for behavioral family therapy unless the recommendation is made in the context of ASAP indications 2-5.

ASAP Clinical Panel*:*

Rationale: In any treatment study of children and adolescents with psychiatric disorders, there will inevitably arise situations that require additional evaluation and/or intervention beyond that provided for in the study protocol. Since this treatment study is being conducted at ten different sites, it is important that there be consistency and agreement in the manner in which these situations are handled, so as not to bias treatment results or to invite site-by-treatment interactions. In some situations, clinical issues that may arise can be anticipated. In others, actions must be taken on an immediate basis. For both situations, common guidelines should be followed for addressing areas of clinical concern. The ASAP Clinical Panel provides a vehicle for a common culture and body of procedures within which events requiring ASAP actions can be considered for action.

Membership: The ASAP Clinical Panel will consist of the following:

- One doctoral level clinical staff member (typically either a PhD or an MD) from each site, chosen by the site PI from among the study clinical staff or primary co-investigators.
- One Coordinating Center clinical staff member (recording clerk) to be designated by the CC PI.

- One NIMH program staff member to be designated by the GPO.

In theory, a conflict-of-interest might arise when the need to terminate a patient for ASAP/clinical reasons collides with the research goals of TADS. **Thus, it is critical to state at the outset that the guiding principle at all times should be to "do no harm" to study patients or their family members and associates.** Given previous experience in the MTA study, which excluded research investigators from ASAP decisions, and the Treatment of Pediatric OCD study, which included them, there appears to be no obvious advantage to excluding PI or Co-I level research staff based on potential conflicts of interest regarding balancing clinical and research needs of TADS subjects. Hence, inclusion of study principal and co-investigators, who are ultimately responsible for the ethical conduct of the study, is considered justifiable in TADS.

Chair. ASAP Panel members will elect a chair and a vice-chair yearly. The chair will conduct the ASAP panel calls; the vice-chair will do so in the absence of the chair.

Quorum. While 2/3 (eight) of the 12 panel members constitute a quorum, an effort will be made to include all Panel members in ASAP concerns so as to ensure consistency among clinical staff.

Tasks: The tasks the ASAP Panel is responsible for include: 1) review and decision-making regarding approaches toward attrition prevention; 2) determination of the need for adjunctive sessions provided by team clinicians; and 3) determination of the need for adjunctive services provided through outside referrals.

Meetings: ASAP Panel meetings will be conducted on a weekly or biweekly basis, depending on the clinical need for meetings, at the completion of regularly scheduled conference calls. While the ASAP panel is charged with cross-site implementation of ASAP procedures, all study personnel can and should be knowledgeable about general ASAP principles, since they may obtain information indicating the need for an ASAP call or session and/or be involved in implementing ASAP-sanctioned interventions.

IV. ASAP Interventions

Requests for ASAP services may occur during various phases of the study. Roughly, the study is divided into four phases:

- Screening Period (approximately 4 weeks from screening call to the beginning of treatment) (2 ASAP sessions allowed)
- Stage I Treatment (weeks 1-12) (2 ASAP sessions allowed)
- Stage II Consolidation/Maintenance (weeks13-18) (2 ASAP sessions allowed)
- Stage III Maintenance (48 weeks) (4 ASAP sessions allowed)
- Stage IV Long-term Follow-up (2 ASAP sessions allowed)

Table 3: ASAP Procedures

ASAP/Stage	Assessment	Discuss Treatment Options	Supportive Counseling	Specific Intervention by TADS	Recommend Intervention Outside TADS
ASAP 1 (Entry)	Yes	No	Yes	No	No
ASAP 2-5	Yes	Yes	Yes	Yes	Yes
ASAP 6 (Stage IV)	Yes	Yes	No	No	Yes
ASAP 7 (Dropout)	Yes	Yes	No	No	No
ASAP 8 (Family)	Yes	Yes	No	No	Yes

Table 3 summarizes ASAP interventions. With the caveat that ASAP interventions are constrained by the ASAP coding system, ASAP Sessions always are tailored to the clinical exigencies.

All ASAP sessions are to be 50 minutes maximum length; phone visits in response to ASAP concerns that last over 20 minutes are to be considered as an ASAP session.

ASAP Phone Procedures

During any study period (entry, I, II, III, IV), anxiety, questions, and concerns over the child's condition or course of treatment can be handled through a maximum of 3 telephone calls per period to the case manager (study entry) or primary clinician (Stages I-IV), with total time not to exceed more than 60 minutes. If calls focus predominantly on explanations of the study, its requirements, and general issues around child management **unrelated to the depressive symptoms,** these initial calls need not have prior approval from the ASAP committee, but should be reviewed during the ASAP Panel calls. The total amount of time for these 3 calls should not be more than 60 minutes, however. Any individual call, which goes on for longer than 20 minutes, requires ASAP review. Any calls or requests for interventions above the total of 60 minutes for 3 calls necessitate approval by the ASAP Panel.

ASAP Interventions Performed by the TADS Team

Using the bank of ASAP sessions, brief specific cognitive-behavioral-family interventions, e.g. panic control training for panic attacks, may be conducted by the patient's pharmacotherapist in pills only conditions or by the psychotherapist in CBT conditions (CBT, COMB) with advance approval of the ASAP panel.

Outside Interventions Not Requiring ASAP

Some interventions are permitted within the framework of in/exclusion criteria, e.g. they may be recommended or simply noted by the treating clinician without the need to invoke ASAP procedures.

1. Child/adolescent continuing a relationship with a school counselor is acceptable provided it is not focused on depression.
2. In-school groups (i.e., friendship groups) are acceptable if they do not have a cognitive behavioral focus (such as social skills training).

3. Testing of the study patient for Learning Disabilities is acceptable.
4. Initiation of academic support services (i.e., LD resource) or tutoring is acceptable.

Outside Interventions Requiring ASAP Approval

Other interventions performed outside the study team (e.g., not from the bank of ASAP sessions) as recommended by the study team (note the exception for subject initiated out-of-protocol interventions) require discussion by the ASAP panel.

1. Any form of individual psychotherapy for the child with a therapist or counselor outside the study.
2. Behaviorally focused intervention groups, such as social skills training, coping with divorce, or anger coping groups, including those in school, outside the study.
3. Family therapy outside the study.
4. Psychotropic medication other than prescribed by TADS.
5. Marital therapy in which management of the subject's mental illness is a primary focus.

Emergency ASAP Interventions

There are emergent situations that require immediate adjunct services such as suicidality, homicidality, abuse or school expulsion. There may also be other emergent situations when a site believes it is necessary to provide adjunct services immediately and that it is not clinically appropriate to wait for approval from the regularly scheduled ASAP Clinical Panel conference.

A **working definition** of such clinical status is: worsening or development of a condition or situation that significantly impairs functioning and/or the conduct of primary treatment and is not covered by other treatment guidelines (e.g., development of a comorbid disorder; child's behavior becoming uncontrollable; worsening of MDD symptoms which severely impede child's functioning and ability to carry out study treatment).

Crises Requiring Immediate Action:

- Suicidal thoughts with intent and/or plan
- Homicidal thoughts with intent and/or plan
- Uncovering of child abuse
- Serious adverse events as defined under adverse event reporting
- Worsening or development of a condition or situation that significantly impairs functioning to the point of requiring immediate clinical attention and/or the conduct of primary TADS treatment(s) and is not covered by other TADS treatment provisions.
- Indications of imminent attrition from TADS for any reason.

These clinical status matters can receive immediate attention after appropriate site deliberations and do not require prior approval by the ASAP Clinical Panel. In the case of an internalizing or externalizing comorbid condition requiring treatment beyond that of the treatment arm, the ASAP Panel may authorize additional ASAP sessions (from the bank of ASAP sessions defined earlier), for example, of specialized behavioral treatment. If additional treatment is needed for

this problem, an outside referral should be made and premature termination procedures implemented.

Note that TADS procedures for managing suicidality are specified in the TADS Suicide Prevention Manual.

Non-emergent ASAP Interventions

Example of routine or "non-emergent" ASAP indications:

- Case management services during entry
- Difficulty engaging subject or family in treatment threatening premature termination
- Need for "out-of-protocol" treatment by TADS team
- Need for "out-of-protocol" treatment outside TADS
- Stage IV case management services

In the event that emotional/behavioral problems associated with MDD or other problems not necessarily related to MDD threaten the ability of an otherwise well qualified subject or family to make it through the entry gates, up to two ASAP sessions may be implemented during the TADS screening phase. If the problem has not abated or stabilized sufficiently to allow progression through the entry gates after two ASAP sessions, the patient should be referred for treatment outside the study and not enrolled in TADS.

As noted earlier, the first two ASAP sessions for emergencies (ASAP 4 or 5) within any study period (screening, Stages I to III or Stage IV) can occur without the prior approval of the ASAP Clinical Panel. These sessions must conform to the treatment guidelines and restrictions for the child's treatment group and avoid cross-contamination. If the problem has not abated after the first two sessions or the problem is non-emergent but is still appropriate for ASAP (e.g. ASAP 2 or 3), the provision of additional adjunct sessions must be approved by the ASAP Clinical Panel.

A maximum of 4 ASAP sessions will be allowed over the course of Stage I and II and another 4 during Stage III. (This is in addition to up to two sessions allowed during the pre-randomization Stage.) Note that ASAP sessions do not "carry over."

For all subjects, an extra session to evaluate the possibility of relapse does not count as an ASAP session unless held primarily to provide an intervention to prevent relapse in which case it should be considered an ASAP session. For subjects in either the medication-only or combined groups, the pharmacotherapist may provide extra sessions to manage side effects without impinging on the ASAP bank of sessions.

If within-arm treatment is not sufficient or entirely appropriate, requests by the clinician that "cross-treatment" action be implemented (for example, the use of medication with a child in the CBT-only group; behavioral programs beyond what is allowed in the pharmacology manual for a child in the medication-only group; the discontinuation of medication or addition of another medication for a child in the combined treatment group) must be presented to the ASAP Clinical Panel to decide on the appropriateness of this action. The Panel will consider the request for additional sessions and/or cross-treatment action, including the review of relevant information provided by the site and will provide specific feedback about actions that can be undertaken.

If a **referral outside of the study** during Stages I, II or III, seems necessary, the issue is brought to the ASAP Clinical Panel who will decide whether or not it is appropriate and will inform the site as to the panel's decision. In cases where the ASAP Panel decides that an outside referral is appropriate, the primary clinician at the requesting site can choose and refer the patient/parent to a suitable clinician or clinical service. The only proviso is that the referral cannot be made to a clinician who is a member of the study team.

In Stage IV, up to two ASAP sessions will be provided. To meet our ethical responsibilities to TADS patients and to assist with "sample maintenance," appropriate crisis/case management should be provided as clinically appropriate. However, treatment will be provided outside the study (i.e., not by TADS team members) through referral to community providers per standard TADS procedures.

V. ASAP During Entry

In the Screening period, the primary goal of ASAP sessions is to respond appropriately to concerns and crises that may emerge prior to the beginning of interventions. Additionally, goals are to prevent attrition prior to the beginning of the study and to limit treatment contamination from additional treatment outside the study setting and from systematic behavioral treatment or medication treatment by the study staff.

After consent is obtained from the family at Gate B, the responsibility for treatment may fall to the study (if initiated by subject's family) until the point of randomization or dropout before randomization. To provide necessary contact during the interval between Gate B and randomization, the treatment teams at the sites will already have assigned a case manager who will be one of the therapists who will later serve as therapist for those assigned to CBT-only and the combined groups. After random assignment to treatment, the case manager for a particular child/family may change, although preferably not. Before randomization, the case manager will: (1) maintain weekly telephone contact; and (2) provide, on an as-needed basis only, up to two crisis-driven treatment sessions. The nature of these sessions will be supportive, non-directive counseling. The overall aim during this time period is to meet clinical responsibilities to the patient by responding appropriately to emergent situations, limit treatment contamination from additional treatment outside the study setting and from systematic behavioral treatment or medication treatment by the study staff, and to prevent attrition.

In general, if family members other than the subject are in need of additional treatment (e.g., maternal depression, paternal alcohol abuse), appropriate referrals may be made to clinical services outside of the study setting. For problems of the study child, e.g., if a school problem is involved, the study team may contact the school, let them know they are aware of the problem and state when assessment will be completed so that treatment can start. All subjects will be treated the same during this time period, i.e., not according to treatment group (they will not have been randomized at this point).

Prototypical ASAP Phone Sessions During Screening

1. Listen, empathize
2. Summarize the nature of the concern.
3. Ask what they have done to deal with the situation.

4. Provide support and encouragement.
5. Address with ASAP committee whether an additional phone contact can address difficulties or whether an ASAP session is needed.
6. Determine with ASAP committee whether an outside referral is needed for other family members.
7. Any phone consultations greater than 20 minutes should be reviewed with the ASAP committee

Prototypical ASAP Visits During Screening

Two ASAP crisis-driven treatment sessions are allowed during the screening period. Attempts will be made to further explain the study, its benefits and risks, and allay concerns in an approved ASAP session with the case manager. Such a session should be conducted in a Rogerian treatment style, in which concerns expressed are reflected back to study patients and/or their family, and empathy is provided. Explanations can be provided for ways treatment studies can be helpful. No procedures for specific MDD management or stress management should be offered during this time.

Treatment requests during this phase of the study may involve outside interventions for marital difficulties, parental substance abuse or psychopathology, or interventions for learning disabilities. Requests for referrals for family members should be documented, but do not need to be reviewed by the ASAP Panel. Conversely, requests for referrals outside TADS for the study subject, e.g. for tutoring or to participate in marital therapy, should first be reviewed with the ASAP Panel per ASAP code 8.

VI. ASAP During Stages I, II and III

During Stages I, II and III, ASAP has the following goals in addition to those listed earlier:

- Where appropriate to continue TADS treatment and assessment procedures, to maintain patients in their assigned treatment arm for the duration of the study when attrition is threatened for any reason.
- When a subject's continued participation in the study is at issue, to address serious concerns that are interfering with study patients' capacity to benefit from study treatment. Some issues may be relevant to the study patient themselves, others to their family members or school circumstances.
- To determine whether other disorders or problems are so severely interfering with the patient's welfare that consideration must be given to removal of the patient from the study protocol so that disorder/problem may be treated as indicated clinically.

During Stages I-III, the lead ASAP member at the site who will field issues first will address ASAP concerns. Then, ASAP concerns will be brought to the ASAP Clinical Panel, which will determine what actions should be taken, and who should be responsible for those actions. A maximum of 4 additional treatment sessions per stage I and II and another 4 during Stage III, may be scheduled on an as needed basis, requiring agreement from the ASAP committee or, in an emergent situation, from the lead ASAP team member at the site and the site PI. Attempts will be made where possible to handle concerns by phone rather than an added session.

ASAP treatment sessions should be reserved for significant worsening of MDD symptoms, increased internalizing symptoms, increased externalized symptoms, significantly decreased school functioning, or a major family crisis impacting the child. An additional session can also be used in the case of threatened attrition from the study. ASAP sessions should be as non-directive as possible. No behavioral techniques should be used in these extra sessions. As much as possible, the MDD symptoms should be ignored, and only the crisis situation addressed.

Example circumstances in which to invoke ASAP phone calls or sessions.

- Despite compliance with treatment, adolescent has significant worsening of MDD symptoms that are interfering with school or home so that parents are threatening to withdraw from the study. When it is not clear whether this is transient or will require premature termination, an additional ASAP intervention session can be scheduled which is supportive in nature, offers reiteration of previously taught skills according to that client's study protocol, or addresses compliance with medication.
- Child has worsening symptoms of an Internalizing Disorder that causes significant impairment in school or home functioning. (Child may be increasingly depressed, have worsening school phobia with school avoidance, have increased fights). Child may now qualify for a different (other than MDD) internalizing disorder as primary. An ASAP supportive therapy session can be conducted; ASAP consideration should assess need for removal from the study or cross-arm treatment if symptoms are so severe as to necessitate alternative treatment.
- Adolescent has worsening symptoms from an Externalizing Disorder, which increases risk for school expulsion or increased family conflict. Per ASAP Panel approval, an ASAP session focusing on general child behavior management around externalizing behaviors can be conducted. MDD cannot be addressed. Rather, establishing and enforcing consistent rules and consequences can be addressed. Support for parents can be given.
- Serious family crisis impacts the family's ability to support child in treatment (i.e., separation, death, and diagnosis of major illness, financial crisis). Per ASAP Panel approval, an ASAP session may be conducted which is supportive in nature and which assists in locating outside resources that would be of help to the family in addressing the immediate crisis.
- Irrespective of clinical status, subject threatens to withdraw consent for treatment but not assessment. Note that this is different from missing some but not all visits, which should be managed within the standard visit framework, e.g. as poor compliance.

In some cases, internal ASAP procedures will not suffice. For example, worsening of symptoms to the point of seriously disrupting school or family functioning (e.g., threatened school expulsion documented by school source or refusal to go to school, running away, sexual promiscuity, worsening substance abuse), may require an alternative or additional intervention outside the study. **Such an intervention may be recommended without exhausting the bank of ASAP interventions and always results when the bank of interventions is exhausted and the clinical situation dictates further treatment outside the study.**

Example situations include:

- Depression symptoms that increase significantly affecting daily impairment or risk of self-harm.

- Serious adverse reaction to medication requiring termination of medication trial and necessitating alternative treatment to both manage the adverse event (recorded on the AEF) and to continue where indicated pharmacological intervention(s) for MDD.
- Concerns regarding mild to moderate medication side effects that raise the question of premature termination from the study. Primarily the treating psychiatrist should address the possibility of early termination (attrition) due to serious medication side effects, but such cases should also be brought to the ASAP panel when more than two extra sessions allowed in the pharmacotherapy protocol have been held and the patient/family are still unsure about whether continued study participation is advisable.
- Indications of development of a serious externalizing disorder which needs to be urgently addressed, including risk of harm to others or carrying a high likelihood of adverse interactions with the juvenile justice system.

Failure to make treatment gains is not a sufficient reason for discontinuing the study. Attempts should be made to get the family through the frustrations of no gains in order to reach the opportunity for full treatment. If family expresses concerns severe enough to discontinue the study, an ASAP session may be conducted to address the families concerns that their needs are not being met by TADS.

VII. ASAP During Stage IV

No ASAP interventions will be made during Stage IV. Assessment and crisis management is permissible even advisable as per the procedures outline for Stage I ASAP, with the goal being to make appropriate treatment recommendations outside the study. In contrast to ASAP recommended treatment in Stages I, II and III, ASAP treatment recommendations in Stage IV can be to TADS team members.

VIII. ASAP Tracking Forms

The ASAP Form codes the reason for ASAP, ASAP codes, recommended intervention and outcome. The PSML codes the indications for and outcome of ASAP for summary transmission to the DSMB.

IX. Summary

ASAP procedures, including the ASAP Panel, provides a consistent vehicle for sites to handle situations that require additional evaluation and/or intervention beyond that provided for in the study protocol. Since this treatment study is being conducted at ten different sites, it is important that there be consistency and agreement in the manner in which these situations are handled, so as not to bias treatment results or to invite site-by-treatment interactions. In some situations, clinical issues that may arise can be anticipated. In others, actions must be taken on an immediate basis. For both situations, common guidelines should be followed for addressing areas of clinical concern. The ASAP Clinical Panel provides a vehicle for a common culture and body of procedures within which events requiring ASAP actions can be considered for action.